



ISSN 2737-971X
eISSN 2737-9752

KNJIGA SAŽETAKA

NACIONALNI KONGRES

6. KONGRES

HEMATOLOGA SRBIJE

ABSTRACT BOOK

NATIONAL CONGRESS

6TH CONGRESS OF

HEMATOLOGISTS OF SERBIA

SERBIAN JOURNAL OF THE MEDICAL CHAMBER

SRPSKI MEDICINSKI ČASOPIS LEKARSKE KOMORE

VOLUMEN 5 • DODATAK III • SEPTEMBAR 2024.

VOLUME 5 • SUPPLEMENT III • SEPTEMBER 2024

ISSN 2737-971X
eISSN 2737-9752

SRPSKI MEDICINSKI ČASOPIS LEKARSKE KOMORE



SERBIAN JOURNAL OF THE MEDICAL CHAMBER

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Dr Subotića 4, p.p. 102, 11129 Beograd, Srbija

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ŠTAMPA: SAJNOS, Novi Sad

TIRAŽ: 200 primeraka

Časopis izlazi 4 puta godišnje

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Website: <https://smj.rs>

PRINTED BY: SAJNOS, Novi Sad

CIRCULATION: 200 copies

The Journal is published quarterly

**LEKARSKA KOMORA SRBIJE
REGIONALNA LEKARSKA KOMORA BEOGRADA**

**NACIONALNI KONGRES
6. KONGRES HEMATOLOGA SRBIJE**

**NATIONAL CONGRESS
6TH CONGRESS OF HEMATOLOGISTS OF SERBIA**



**KNJIGA SAŽETAKA
ABSTRACT BOOK**

**Hotel Crowne Plaza, Beograd
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EDITORIJAL



Drage kolegice i kolege,

Velika nam je čast i zadovoljstvo da vam predstavimo Knjigu sažetaka 6. Kongresa hematologa Srbije, koja sadrži najnovije rezultate istraživanja i dostignuća u oblasti hematologije u našem regionu. Ovo okupljanje pruža jedinstvenu priliku za razmenu znanja i iskustava među stručnjacima iz naše zemlje i okruženja, a verujemo da će doprineti daljem napretku i inovacijama u hematologiji.

Svi sažeci uključeni u ovu knjigu prošli su rigoroznu recenziju od strane Naučnog odbora kongresa. Odbor, sastavljen od istaknutih istraživača i profesora sa bogatim iskustvom, temeljno je pregledao i ocenio svaki rad kako bismo osigurali da izloženi rezultati zadovoljavaju visoke naučne standarde. Ovaj proces garantuje da predstavljeni sadržaji doprinose postojećem znanju i nude nove perspektive i pristupe u dijagnostici i lečenju hematoloških stanja.

Ovom prilikom želimo da izrazimo duboku zahvalnost svim autorima na njihovom trudu i posvećenosti, kao i recenzentima za njihove stručne savete i smernice koje su znatno doprinele kvalitetu prezentovanih radova. Njihova kolektivna posvećenost osnova je uspeha našeg kongresa i unapređenja naše zajedničke misije – boljeg razumevanja i lečenja hematoloških bolesti kako malignih tako i benignih.

Očekujemo da će diskusije i ideje iznete tokom ovog kongresa inspirisati nove projekte i podstaknuti saradnju među institucijama, kako bismo zajedno prevazišli izazove sa kojima se suočavamo i unapredili zdravstvenu zaštitu pacijenata. Verujemo da će vam sadržaj ove knjige sažetaka poslužiti kao koristan resurs i izvor novih saznanja.

Zahvaljujemo se svim učesnicima na njihovom doprinosu i želimo vam uspešan kongres.

*Predsednik Naučnog odbora Kongresa
Prof. dr Andrija Bogdanović*

*Predsednik Kongresa
Prof. dr Darko Antić*

EDITORIAL



Dear colleagues,

It is our great honor and pleasure to present the Abstract Book for the 6th Congress of Hematologists of Serbia, which contains the latest research results and achievements in the field of hematology in our region. This gathering provides a unique opportunity to exchange knowledge and experiences among experts from our country and its surroundings, and we believe it will contribute to further advancements and innovations in hematology.

All abstracts included in this book have undergone a rigorous review process by the Scientific Committee of the congress. The committee, composed of distinguished researchers and professors with extensive experience, meticulously reviewed and evaluated each paper to ensure that the presented results meet high scientific standards. This process guarantees that the presented content contributes to existing knowledge and offers new perspectives and approaches in the diagnosis and treatment of hematological conditions.

On this occasion, we wish to express our deep gratitude to all the authors for their effort and dedication, as well as to the reviewers for their expert advice and guidance, which have significantly contributed to the quality of the presented works. Their collective commitment is the foundation of our congress's success and of our shared mission – a better understanding and treatment of both malignant and benign hematological diseases.

We expect that the discussions and ideas presented during this congress will inspire new projects and foster collaboration among institutions so that together we can overcome the challenges we face and improve patient care. We believe that the content of this Abstract Book will serve as a valuable resource and source of new knowledge.

We thank all participants for their contributions and wish you a successful congress.

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AKUTNE LEUKEMIJE

ACUTE LEUKEMIA

ZNAČAJ IMUNOFENOTIPSKIH MARKERA ZA DIFERENCIJALNU DIJAGNOZU AKUTNE PROMIJELOCITNE LEUKEMIJE OD AKUTNE MIJELOIDNE LEUKEMIJE SA NPM1^{mut}

THE SIGNIFICANCE OF IMMUNOPHENOTYPIC MARKERS FOR THE DIFFERENTIAL DIAGNOSIS OF ACUTE PROMYELOCYTIC LEUKEMIA FROM ACUTE MYELOID LEUKEMIA WITH NPM1^{mut}

Tijana Dragović Ivančević¹, Nada Kraguljac-Kurtović¹, Vesna Knežević¹, Sandra Bižić-Radulović¹,
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SAŽETAK

Uvod: Akutna promijelocitna leukemija (APL) deli imunofenotipske karakteristike sa jednom od varijanti akutne mijeloidne leukemije sa NPM1 mutacijom (AML/NPM1mut).

Cilj: Utvrđivanje imunofenotipskih markera značajnih za diferencijalnu dijagnozu APL od AML/NPM1mut.

Metode: Ispitivanje je sprovedeno kod 124 bolesnika sa de novo APL (95/124) i AML/NPM1mut (29/124). Uzorci koštane srži su obeležavani primenom 6-8-kolornih panela monoklonskih antitela. Analiza uzoraka je urađena na protočnom citometru BD FACSCantoII (BD Biosciences, USA), BD FACSDiva softver. Leukocitni molekul je smatran pozitivnim ukoliko je utvrđena ekspresija na $\geq 20\%$ leukemij-skih ćelija za membranske, odnosno $\geq 10\%$ citoplazmatske (cit) molekule.

Rezultati: Molekul CD34 je eksprimiran sa niskom učestalošću (APL, 20% vs. AML/NPM1mut, 7%), a CD117 sa visokom učestalošću (APL, 98% vs. AML/NPM1mut, 100%). Značajno višu učestalost ekspresije u APL u odnosu na AML/NPM1mut su ispoljili molekul: CD13 (100% vs. 86%, $p = 0,003$), CD114 (96% vs. 56%, $p = 0,001$), citLizozim (91% vs. 62%, $p = 0,001$) i CD64 (86% vs. 34%, $p < 0,001$). Značajno nižu učestalošću ekspresiju u APL u odnosu na AML/NPM1mut su ispoljili molekul: HLA-DR (4% vs. 48%, $p < 0,001$), CD11a (9% vs. 78%, $p < 0,001$) i CD11c (1% vs. 93%, $p < 0,001$). Limfoidni molekul su eksprimirani sa niskom učestalošću: APL (CD2, 20%; CD56, 12%; CD7, 0%) odnosno AML/NPM1mut (CD2, 0%; CD56, 14%; CD7, 17%). Statistički značajna razlika je utvrđena u slučaju molekula CD2 ($p = 0,030$) i CD7 ($p < 0,001$).

Zaključak: Grupa molekula koja definiše specifičan imunofenotip APL (CD117+/CD34-/HLA-DR-/CD114+/citLizozim+/CD64+/CD11a-/CD11c-/CD2-/+) se značajno razlikuje od grupe koji definišu specifičan imunofenotip AML/NPM1mut (CD117+/CD34-/HLA-DR-/CD114+/citLizozim+/CD64-/CD11a+/CD11c+/CD7-/).

Ključne reči: APL, AML sa NPM1mut, imunofenotipizacija, protočna citometrija

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ABSTRACT

Introduction: Acute promyelocytic leukemia (APL) has similar immunophenotype as one of the variants of acute myeloid leukemia with NPM1 mutation (AML/NPM1mut).

Objective: Identification of relevant immunophenotypic markers for the differential diagnosis of APL from AML/NPM1mut.

Methods: The study included 124 patients with de novo APL (95/124) and AML/NPM1mut (29/124). Bone marrow samples were labeled using 6-8-color panels of monoclonal antibodies. Analysis was performed on a flow cytometer BDFACS CantoII (BD Biosciences, USA), BD FACSDiva software. Molecules were considered positive if $\geq 20\%$ of the cells expressed the molecule on the membrane, and $\geq 10\%$ in the cytoplasm (cyt).

Results: The CD34 was expressed with a low frequency (APL, 20% vs. AML/NPM1mut, 7%), and CD117 with a high frequency (APL, 98% vs. AML/NPM1mut, 100%). Molecules with significantly higher frequency in APL compared to AML/NPM1mut were: CD13 (100% vs. 86%, $p = 0.003$), CD114 (96% vs. 56%, $p = 0.001$), cytochrome (91% vs. 62%, $p = 0.001$) and CD64 (86% vs. 34%, $p < 0.001$). Molecules with significantly lower frequency in APL compared to AML/NPM1mut were: HLA-DR (4% vs. 48%, $p < 0.001$), CD11a (9% vs. 78%, $p < 0.001$) and CD11c (1% vs. 93%, $p < 0.001$). Lymphoid molecules showed low frequency: APL (CD2, 20%; CD56, 12%; CD7, 0%) and AML/NPM1mut (CD2, 0%; CD56, 14%; CD7, 17%). A significant difference was found for CD2 ($p = 0.030$) and CD7 ($p < 0.001$).

Conclusions: Leukocyte molecules that define the specific immunophenotype of APL (CD117+/CD34-/HLA-DR-/CD114+/citLizozim+/CD64+/CD11a-/CD11c-/CD2-/+) were significantly different from the group that define AML/NPM1mut (CD117+/CD34-/HLA-DR-/CD114+/citLizozim+/CD64-/CD11a+/CD11c+/CD7-/).

Keywords: APL, AML with NPM1mut, immunophenotyping, flow cytometry

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PRVO ISKUSTVO U PRIMENI AZACITIDINA KOD PACIJENATA SA AKUTNOM MIJELOIDNOM LEUKEMIJOM (AML), MIJELODOSPLASTIČNIM SINDROMOM (MDS) I HRONIČNOM MIJELOMONOCITNOM LEUKEMIJOM (CMML)

FIRST EXPERIENCE IN THE USE OF AZACITIDINE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA (AML), MYELODOSPLASTIC SYNDROME (MDS) AND CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

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SAŽETAK

Uvod: Azacitidin se primenjuje u lečenju pacijenata sa AML, MDS srednjeg-2 i viskog stepena rizika i CMML kod kojih nije indikovana transplantacija matične ćelije hematopoeze.

Cilj: Cilj rada je retrospektivna analiza toka i ishoda lečenja „unfit“ AML pacijenata, pacijenata sa MDS-om i CMML-om lečenih monoterapijom azacitidinom.

Metode: Analizirano je 30 pacijenata nakon primene azacitidin amp 75 mg/m² d1-d7 s.c./dn na 28 dana na Odeljenju akutnih leukemija od maja 2021. do juna 2024. Azacitidin je prvi put primenjen kod navedenih pacijenata 2021.

Rezultati: U ispitivanoj grupi bilo je 12/30 (40%) pacijenata ženskog i 18/30 (60%) muškog pola, srednje starosne dobi od 67 godina (46–76). AML je imalo 10 pacijenata, MDS 15 pacijenata (MDS-EB2-5; MDS-EB1-8; MDS-MLD-2) i CMML 5 pacijenata (CMML-1-2; CMML-2-3). Medijana primenjenih ciklusa azacitidina bila je 6 (1–25). Nakon 6 ciklusa terapije mijelogram je pokazao CR kod 4/10 (40%) i stabilnu bolest kod 3/10 (30%) kod pacijenata sa AML; CR 6/15 (40%) i PR 3/15 (20%) kod MDS-a; CR kod 3/5 (60%) i PR 1/5 (20%) kod CMML. Preminulo 10 pacijenata (33,3%); AML 3, MDS 6 i CMML 1. Poboljšanje kvaliteta života i smanjenje transfuzione zavisnosti konstatovani u sve tri grupe pacijenata koji su postigli odgovor na terapiju. Zbog prolongirane pancitopenije doza leka je redukovana za 50% kod 2/10 pacijenata sa AML i kod 2/15 sa MDS-om. Medijana preživljavanja je 13 meseci (6–48 meseci).

Zaključak: Primena azacitidina u AML, MDS-u i CMML-u daje obećavajuće rezultate kako u postizanju ukupnog odgovora, tako i smanjenju transfuzione zavisnosti.

Ključne reči: azacitidin, AML, MDS, CMML

ABSTRACT

Introduction: Azacitidine is used in the treatment of patients with AML, intermediate-2 and high-risk MDS, and CMML in whom hematopoietic stem cell transplantation is not indicated.

Objective: The aim of the work is a retrospective analysis of the course and outcome of the treatment of unfit AML patients, patients with MDS and CMML treated with azacitidine monotherapy.

Methods: 30 patients were analyzed after the administration of azacitidine amp 75 mg/m² d1-d7 s.c./day for 28 days at the Department of Acute Leukemia from May 2021 to June 2024. Azacitidine was used for the first time in the mentioned patients in 2021.

Results: In the examined group, there were 12/30 (40%) female and 18/30 (60%) male patients, with a mean age of 67 years (46–76). 10 patients had AML, 15 had MDS and 5 had CMML. The median number of azacitidine cycles used was 6 (1–25). After 6 cycles of therapy myelogram showed CR in 4/10 (40%) and stable disease in 3/10 (30%) AML; CR 6/15 (40%), PR 3/15 (20%) in MDS; CR in 3/5 (60%), PR 1/5 (20%) in CMML. 10 patients died (33.3%). Improvement of the quality of life and reduction of transfusion dependence were noted in all three groups of patients. Due to prolonged pancytopenia, the drug dose was reduced by 50% in 2/10 patients with AML and 2/15 with MDS. Median survival is 13 months (6–48).

Conclusion: The use of azacitidine in AML, MDS and CMML gives promising results both in achieving an overall response and in reducing transfusion dependence.

Keywords: azacitidine, AML, MDS, CMML

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USE OF VENETOCLAX IN THE TREATMENT OF PATIENT WITH MIXED LINEAGE LEUKEMIA (MPAL), CASE REPORT

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SAŽETAK

Uvod: Incidenca akutne mijeloidne leukemije (AML) raste kod pacijenata starijih od 60 godina. Petogodišnje preživljavanje pacijenata starosti 65–74 godine je 10,8%, a iznad 75 godina 2,7%. U lečenju novodijagnostikovanih „unfit“ AML pacijenata primenjuje se venetoklaks i azacitidin (CR i CRi kod 60–67% pacijenata, medijana preživljavanja 9,6 meseci; 7,2–12,4).

Cilj: Prikazati pacijenta sa akutnom leukemijom mešovutih linija (MPAL) kod koga je prvi put primenjena terapija venetoklaks + azacitidin na Odeljenju akutnih leukemija Klinike za hematologiju UKCS.

Prikaz slučaja: U oktobru 2023. kod pacijenta muškog pola, 76 godina, postavljena je dg. MPAL, T/mijeloidna varijanta CD56+, 47–50, XY, kompleksne aberacije [cp11], FLT3-ITD negativan, NPM1 negativan, bez neuroleukemije, adverse risk, ECOG PS 1, AML-CM score 4. Inicijalna krvna slika Hgb 73 g/L, Le 1,1x10⁹/L, Trc 58x10⁹/L. Primenjena Th. venetotoklaks tbl D1 100 mg, D2 200 mg, D3-28 400 mg p.o./dn i azacitidin amp 75 mg/m² d1-d7 s.c./dn sa prolongiranim pancitopenijom. U novembru 2023. težak oblik COVID-19 infekcije i nastavak terapije odložen 2,5 meseca. U januaru i aprilu 2024. primenjena još dva ciklusa venetoklaks (d1-d15) + azacitidin, uz dobru toleranciju i normalizaciju krvne slike nakon jatrogene aplazije. Mijelogram nakon tri ciklusa terapije pokazao je parcijalnu remisiju. U junu 2024. usled komplikacija urinarne infekcije i sepse, exitus letalis nastupa 9,5 meseci od postavljanja dijagnoze MPAL.

Zaključak: Kombinacija venetoklaksa i azacitidina kod novodijagnostikovanih „unfit“ AML pacijenata u odnosu na standardnu terapiju je u prednosti kako u postizanju CR+CRi, tako i ukupnom preživljavanju.

Cljučne reči: AML, MPAL, venetoklaks, azacitidin

ABSTRACT

Introduction: The incidence of acute myeloid leukemia (AML) increases in patients over 60 years of age. Five year survival of patients aged 65–74 years is 10.8% and over 75 years 2.7%. Venetoclax and azacitidine are used in the treatment of newly diagnosed „unfit“ AML (CR+CRi in 60–67% of patients, median survival 9.6 months; 7.2–12.4).

Objective: To present a patient with mixed lineage acute leukemia (MPAL) who was first administered venetoclax + azacitidine therapy at the Acute Leukemia Department of the Clinic of Hematology UCCS.

Case report: In October 2023, a 76-year-old male patient was diagnosed with MPAL, T/myeloid variant CD56+, 47-50, XY, complex aberrations [cp11], FLT3-ITD negative, NPM1 negative, no neuroleukemia, adverse risk, ECOG PS 1, AML-CM score 4. Initial blood count Hgb 73 g/L, Le 1.1x10⁹/L, Trc 58x10⁹/L. Applied th. venetotokax tbl D1 100 mg, D2 200 mg, D3-28 400 mg p.o. day and azacitidine amp 75 mg/m² d1-d7 s.c./day with prolonged pancytopenia. In November 2023, severe form of covid 19 infection and continuation of therapy delayed for 2.5 months. In January and April 2024, two more cycles of venetoclax (d1-d15) + azacitidine were applied, with good tolerance and normalization of the blood count after iatrogenic aplasia. A myelogram after three cycles of therapy showed a partial remission. In June 2024, due to complications of urinary infection and sepsis, exitus lethalis occurs 9.5 months after the diagnosis of MPAL.

Conclusion: The combination of venetoclax and azacitidine in newly diagnosed unfit AML patients compared to standard therapy is advantageous both in achieving CR+CRi and overall survival.

Keywords: AML, MPAL, venetoclax, azacitidine

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TREATMENT OF YOUNG ADULT ACUTE LYMPHOBLASTIC
LEUKEMIA PATIENTS USING PEDIATRIC PROTOCOLS – EXPERIENCE
OF THE UNIVERSITY CLINICAL CENTER OF SERBIA

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SAŽETAK

Uvod: Lečenje akutne limfoblastne leukemije (ALL) mlađih odraslih pacijenata (≤ 40 –45 godina) pedijatrijskim protokolima pokazalo je veće stope kompletnih remisija (KR) i duže ukupno preživljavanje (engl. overall survival (OS)) u odnosu na istorijske protokole.

Cilj: procena stope KR, relapsa, OS i komplikacija kod ALL bolesnika lečenih pedijatrijskim protokolom

Metode: 11 bolesnika sa ALL lečenih u Univerzitetskom kliničkom centru Srbije HOVON100 protokolom (jun 2022. – mart 2024). Na dijagnozi određivani su standardni laboratorijski i za leukemiju vezani parametri. KR smatrana je $< 5\%$ blasta u koštanoj srži, a negativnom merljivom rezidualnom bolesti (MRB) $< 0,01\%$ u srži. Praćene su komplikacije lečenja i OS.

Rezultati: 7/4 (64/36%) žena/muškaraca, common-B-ALL 8 (73%), 2 (18%) proB i 1 (9%) T; 10/11 (91%); 10/11- visokog rizika. KR je postignuta u 100%, sa MRB+ u 2/11 (18%) pacijenata i jedan relaps (9%). Lečenje se komplikovalo: infekcijom (100%), koagulopatijom (8 (73%)), trombozom kod (1 (9%)); hepatotoksičnošću (8 (73%)), poremećajem lipidograma (2 (18%)) i hipersenzitivnošću na asparaginazu (1 (9%)). Transplantirano je 5 (45%) pacijenata. Medijana OS: 11 meseci (opseg: 5–26). Stopa preživljavanja bila je 55%; petoro je preminulo od infekcije (3/2 tokom terapije/transplantacije). Značajno niže medijane inicijalnog broja trombocita $21 \times 10^9/L$ (opseg: 10–48), odnosno $89 \times 10^9/L$ (opseg: 36–223), bile su u preminulih, u odnosu na preživele ($p = 0,017$).

Zaključak: početni rezultati lečenja HOVON100 protokolom pokazali su stopototnu KR, dominantno MRD-, značajno veću stopu preživljavanja od 55% u odnosu na istorijske protokole (22–40%), uz nešto višu stopu smrtnosti vezane za terapiju i inicijalnu trombocitopeniju teškog stepena kao potencijalni prediktor lošeg ishoda lečenja.

Ključne reči: HOVON100, akutna limfoblastna leukemija, preživljavanje, kompletna remisija, toksičnost

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ABSTRACT

Introduction: Treatment of acute lymphoblastic leukemia (ALL) in younger adult patients (≤ 40 –45 years) with pediatric protocols showed higher complete remissions rates (CR) and longer overall survival (OS) compared to historical protocols.

Objective: Assessment of CR rate, relapse, OS and complications in ALL patients treated with pediatric protocol.

Methods: 11 patients with ALL treated at the University Clinical Center of Serbia with HOVON100 protocol (June 2022 – March 2024). At diagnosis, standard laboratory and leukemia-related parameters were determined. CR was defined $< 5\%$ blasts in the bone marrow, and negative measurable residual disease (MRD) $< 0.01\%$ in the bone marrow. Treatment complications and OS were monitored.

Results: 7/4 (64/36%) female/male, common-B-ALL 8 (73%), 2 proB (18%) and 1 T (9%); 10/11 (91%)- high risk. CR: in 100%, with MRD+ in 2/11 (18%) with one relapse (9%). Treatment was complicated by: infection (100%), coagulopathy (8 (73%)), thrombosis (1 (9%)); hepatotoxicity (8 (73%)), lipid metabolism disturbance (2 (18%)) and hypersensitivity to asparaginase (1 (9%)); 5 (45%) patients underwent transplantation. Median OS: 11 months (range: 5–26). Survival rate was 55%; five died of infection (3/2 during therapy/transplantation). A statistically significant difference was observed regarding the initial platelet count $21 \times 10^9/L$ (range: 10–48) vs. $89 \times 10^9/L$ (range: 36–223) compared between the deceased and surviving group ($p = 0.017$).

Conclusion: Initial results of treatment with the HOVON100 protocol showed 100% CR, predominantly MRD-, a significantly higher survival rate of 55% compared to historical protocols (22–40%), with a slightly higher rate of treatment-related mortality and initial severe thrombocytopenia as a potential predictor of poor treatment outcome.

Keywords: HOVON100, acute lymphoblastic leukemia, survival, complete response, toxicity

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ANTIBIOTIC RESISTANCE PATTERN OF MULTIDRUG RESISTANT BACTERIA IN ACUTE MYELOID LEUKEMIA PATIENTS DURING INDUCTION TREATMENT

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SAŽETAK

Uvod: Infekcije ostaju glavni uzrok morbiditeta i mortaliteta tokom indukciono terapije akutne mijeloidne leukemije (AML). Istraživanje multi-rezistentnih bakterija (MDR) postaje sve značajnija tema zbog njihove rastuće prevalencije.

Cilj: Cilj našeg istraživanja bio je procena stepena rezistencije bakterija na antibiotike kod pacijenata koji su primili intenzivnu indukcionu terapiju i da ispitamo faktore rizika za razvoj MDR infekcija.

Metode: Sprovedena je retrospektivna analiza infektivnih komplikacija kod 40 pacijenata sa AML koji su leženi indukcionom terapijom i hospitalizovani između januara 2022. i decembra 2023. u jedinici intenzivne nege. Multi-rezistencija na lekove (MDR) i ekstenzivna rezistencija na lekove (XDR) definisani su prema zajedničkom izveštaju Evropskog centra za kontrolu bolesti (ECDC) i CDC-a.

Rezultati: Među 40 pacijenata sa 47 bakterijskih izolata, *Enterococcus* spp. je bila najčešća Gram pozitivna bakterija (27,6%), od kojih je 76,92% bilo otporno na vankomicin, bez uočene rezistencije na tigeciklin i linezolid. Najčešća Gram negativna bakterija, *Klebsiella pneumoniae* (19,1%) je bila otporna na cefalosporine, karbapeneme, hinolone (88,89%), dok je rezistencija na ceftazidim/avibaktam i kolistin bila manje izražena (20%, odnosno 44,4%). MDR i XDR bakterije su izolovane u 59,5%, odnosno 42,5% slučajeva. Faktori rizika za razvoj MDR infekcija su bili: niži broj leukocita ($p = 0,023$); LDH $> 1,5\times$ ($p = 0,036$); respiratorna podrška ($p = 0,003$). Stopa mortaliteta direktno uzrokovana infekcijom kod pacijenata sa izolovanim MDR sojevima je iznosila 35,7%.

Zaključak: Naši rezultati pokazuju učestale MDR i XDR bakterijske infekcije u indukcionoj terapiji pacijenata sa AML, što naglašava potrebu za daljim razmatranjem profilaktičke i empirijske upotrebe antibiotika.

Ključne reči: multi-rezistentne bakterije, infekcija, AML

ABSTRACT

Introduction: Infections remain a major cause of morbidity and mortality during induction treatment of acute myeloid leukemia (AML). The surge of multi-drug resistant bacteria (MDR) has sparked an interest in research on this topic in recent years.

Objective: The aim of our research was to evaluate antibiotic resistance patterns of bacteria in patients undergoing induction treatment and susceptibility factors for developing MDR infections.

Methods: A retrospective analysis of infectious complications was performed in 40 patients with AML undergoing induction therapy hospitalized between January 2022 and December 2023 in the intensive care unit (ICU). MDR and extensive drug-resistance (XDR) were defined according to the joint European Center for Disease Control (ECDC) and CDC report.

Results: From 40 patients and 47 bacterial isolates, *Enterococcus* spp. was the most frequent Gram-positive bacterium (27.6%), showing a 76.92% resistance rate to vancomycin, without resistance to tigecycline and linezolid. The most common Gram-negative bacteria, *Klebsiella pneumoniae* (19.1%), was resistant to cephalosporins, carbapenems, quinolones (88.89%), while exhibiting a lower resistance rate to ceftazidime/avibactam and colistin (20% and 44.4% respectively). MDR and XDR bacteria were detected in 59.5% and 42.5%, respectively. Risk factors for developing MDR infections were: lower leukocyte counts ($p = 0.023$); LDH > 1.5 ($p = 0.036$); respiratory support ($p = 0.003$). Patients with MDR strains had a mortality rate of 35.7% due to infections.

Conclusion: Our results demonstrate frequent MDR and XDR bacterial infections in induction therapy of AML patients which highlights the need for reevaluating prophylactic, empirical antibiotic use.

Keywords: multi-drug resistant bacteria, infections, AML

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GENETIC ABERRATION IN ADULT PATIENTS WITH ACUTE B-LYMPHOBLASTIC LEUKEMIA

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SAŽETAK

Uvod: Akutna B-limfoblastna leukemija (B-ALL) je maligna bolest nastala usled genetičkih aberacija u B-limfoidnom progenitoru. Genetičke metode su moćan alat za otkrivanje ovih genetičkih aberacija, koje su ključne za dijagnozu, klasifikaciju, prognozu i lečenje B-ALL.

Cilj: Analiza tipova i učestalosti genetičkih aberacija kod bolesnika B-ALL.

Metode: Rad prikazuje rezultate genetičkih analiza u grupi od 136 bolesnika sa de novo B-ALL, koji su dijagnostifikovani na Klinici za hematologiju, UKCS u periodu 2014–2024. godina. Citogenetička analiza je rađena na nestimulisanim ćelijama koštane srži tehnikom HG traka. Kod 100 bolesnika, metodom reverzne transkripcije lančane reakcije polimeraze (RT-PCR) je analizirano prisustvo BCR-ABL1 genskog rearanžmana.

Rezultati: U grupi od 136 bolesnika, medijane starosti 52 godine (19–80 godina), predominirale su osobe ženskog pola (55%). Citogenetičku analizu nije bilo moguće uraditi kod 7 (5,1%) bolesnika. Kod bolesnika sa validnom citogenetičkom analizom, 64,3% (83/129) je imalo aberantan kariotip. Najčešće detektovane rekurentne hromozomske aberacije su: t(9;22)(q34;q11) (27,1%), hiperdiploidni kariotip (12,4%) i t(4;11)(q21;q23) (7,7%). Kod starijih bolesnika (> 40 godina) je utvrđena veća učestalost t(9;22)(q34;q11), koja je često udružena sa dodatnim hromozomskim aberacijama. Kod bolesnika sa potvrđenom fuzijom BCR-ABL1, 64,6% je imalo minor (e1a2), a 32,2% major (b2a2 ili b3a2) tip rearanžmana. Jedan bolesnik (3,2%) je imao koekspresiju minor i major BCR-ABL1 rearanžmana.

Zaključak: Rezultati su pokazali da 64,3% bolesnika sa B-ALL na dijagnozi ima aberantan kariotip. Naši bolesnici kao najčešću aberaciju imaju t(9;22)(q34;q11) i minor (e1a2) tip rearanžmana. Većina naših bolesnika sa B-ALL na dijagnozi ima aberacije koje predstavljaju loš prognostički parametar.

Ključne reči: akutna B-limfoblastna leukemija, citogenetička analiza, hromozomske aberacije, BCR-ABL1 rearanžma

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ABSTRACT

Introduction: Acute B-lymphoblastic leukemia (B-ALL) is a malignant disease caused by various genetic aberrations in B-lymphoid progenitor cells. Genetic methods are powerful tools for detection of these genetic aberrations and represent the most important criteria for diagnosis, classification, prognosis, and treatment of B-ALL.

Objective: The aim of this study is identification of types and frequencies of genetic aberrations in B-ALL patients.

Methods: HG-band karyotyping was used on non-stimulated cells of bone marrow of 136 de novo B-ALL patients, diagnosed in Clinic of Hematology, UCCS between 2014–2024. In 100 patients, BCR-ABL1 gene rearrangement detection was done using a reverse transcriptase-polymerase chain reaction (RT-PCR) based technique.

Results: In the group of 136 patients, the median age was 52 (range 19–80), females predominated (55%). Due to an absence of dividing cells, cytogenetic analysis was not possible for 7 (5.1%) patients. Among analyzed patients, an aberrant karyotype was detected in 83 (64.3%). The most frequently detected recurrent chromosomal aberrations were: t(9;22)(q34;q11) (27.1%), hyperdiploid karyotype (12.4%), and t(4;11)(q21;q23) (7.7%). In older patients (> 40 years) a higher frequency of t(9;22)(q34;q11) was found, usually associated with additional chromosomal aberrations. RT-PCR analysis confirmed BCR-ABL1 gene rearrangement in 31 patients, including 64.6% with minor (e1a2), 32.2% with major (b2a2 or b3a2), and 3.2% patients with coexpression of both BCR-ABL1 rearrangements.

Conclusion: Aberrant karyotype was detected in 64.3% of B-ALL patients, with t(9;22)(q34;q11) being the most common chromosomal aberration and minor (e1a2) being the most common type of BCR-ABL1 rearrangement. Overall, most of B-ALL patients had genetic aberrations that are poor prognostic factors.

Keywords: acute B-lymphoblastic leukemia, cytogenetic analysis, chromosomal aberration, BCR-ABL1 rearrangement

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LEUKAPHERESIS DOES NOT HAVE NA IMPACT ON EARLY MORTALITY RATE IN ACUTE MYELOID LEUKEMIA PATIENTS WITH HYPERLEUKOCYTOSIS

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SAŽETAK

Uvod: Hiperleukocitoza i leukostaza kod bolesnika sa akutnom mijeloidnom leukemijom (AML) su prediktori lošeg ishoda i rane smrtnosti, i predstavljaju urgentno stanje koje zahteva hitnu intervenciju. Uloga leukocitafereze (LA) u zbrinjavanju hiperleukocitarne AML još uvek je predmet intenzivnih rasprava.

Cilj: Ispitivanje kliničkih karakteristika bolesnika sa AML kod kojih je sprovedena LA u poređenju sa onima kod kojih nije (ne-LA) i ishoda u okviru 15, 30 i 90 dana.

Metode: Retrospektivnom studijom obuhvaćeni su adultni bolesnici sa AML koji su dijagnostikovani i lečeni u periodu 2014–2023. Bolesnici sa hiperleukocitozom ($Le > 100 \times 10^9/L$) su na osnovu terapijskog pristupa podeljeni u dve grupe: LA vs. ne-LA. Indikacija za sprovođenje LA je bila prisustvo simptomatske bolesti.

Rezultati: Od ukupno 526 uzastopnih novodijagnostikovanih AML pacijenata, 49 (9,3%) je na prezentaciji imalo hiperleukocitarnu AML. Citoredukcija je primenjena kod 40/49 (81,6%) bolesnika, dok je LA sprovedena kod 9/49 (18,4%) bolesnika. Bolesnici u LA grupi su imali značajno veći broj Le u odnosu na ne-LA grupu ($p = 0,024$), ali nije uočena statistički značajna razlika u pogledu: ECOG-PS, HCT-Cl, broja trombocita, ISTH DIC skor ≥ 5 , LDH $> 5N$, procenta blasta u PK i KS, FLT3-ITDmut, NPM1mut, CD56+ i CD11c+ ($p < 0,05$). Nije uočena statistički značajna razlika u OS ($p = 0,885$), kao i stopi smrtnosti na dan 15 (33,3% vs. 25%, $p = 0,570$), dan 30 (55,6% vs. 35%; $p = 0,243$) i dan 90 (25% vs. 55%, $p = 0,571$) između LA vs. ne-LA grupe.

Zaključak: Iako LA omogućava brzo smanjenje tumorske mase, ne poboljšava stopu rane smrtnosti u hiperleukocitarnoj AML. Potrebna su dalja istraživanja da bi se utvrdila podgrupa bolesnika sa hiperleukocitozom kod kojih bi ova procedura imala koristi.

Ključne reči: akutna mijeloidna leukemija, hiperleukocitoza, citoredukcija, leukocitafereza

ABSTRACT

Introduction: Hyperleukocytosis and leukostasis in AML is a hematologic emergency which requires prompt intervention. It is associated with high early mortality rate and poor outcomes. The role of leukapheresis (LA) in hyperleukocytic AML management is still highly debated.

Objective: The aim was to evaluate clinical characteristics and outcomes within 15, 30 and 90 days between patients who underwent LA and non-LA treated patients.

Methods: A retrospective study included de novo AML patients > 18 years, with hyperleukocytosis ($WBC > 100 \times 10^9/L$), diagnosed and treated between 2014–2023. The patients were divided in two groups based on therapeutic approach (LA vs. non-LA). The decision to perform emergency LA was based on the presence of symptomatic disease.

Results: Out of 526 consecutive de novo AML patients, we identified 49 (9.3%) with hyperleukocytic AML. Cyto-reduction was conducted in 40/49 (81.6%) patients and LA was performed in 9/49 (18.4%) patients. Patients who underwent LA had significantly higher WBC count compared to non-LA group, $p = 0.024$, but no significant difference was observed regarding: ECOG-PS, HCT-Cl, platelet count, ISTH DIC score ≥ 5 , LDH $> 5N$, blast percentage in PB and BM, FLT3-ITD-mut, NPM1mut, CD56+ and CD11c+ ($p < 0.05$). There was no significant difference in overall survival ($p = 0.885$), nor in mortality rate on day 15 (33.3% vs. 25%, $p = 0.570$), day 30 (55.6% vs. 35%; $p = 0.243$) and day 90 (25% vs. 55%, $p = 0.571$) in LA vs. non-LA group.

Conclusion: Although LA allows rapid and efficient tumor debulking, it does not improve early mortality rate in AML patients with hyperleukocytosis. Further studies are needed to determine subgroup of patients with hyperleukocytosis who might benefit from this procedure.

Keywords: acute myeloid leukemia, hyperleukocytosis, cyto-reduction, leukapheresis

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BLEEDING PREDICTORS IN PATIENTS WITH ACUTE MYELOID LEUKEMIA

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SAŽETAK

Uvod: Krvarenje je jedan od najčešćih uzroka rane smrtnosti obolelih od akutne mijeloidne leukemije (AML).

Cilj: Procena incidencije i identifikacija prediktora krvarenja na dijagnozi i tokom prvih 30 dana od dijagnoze kod obolelih od AML.

Metode: Sprovedena je retrospektivna analiza odraslih pacijenata sa dijagnozom AML (pacijenti sa akutnom promijelocitnom leukemijom su isključeni) kod kojih je dijagnoza postavljena između 2009 i 2023. godine. Prikupljeni su demografski, inicijalni kliničko-laboratorijski i podaci vezani za primenjenu terapiju. Za analizu podataka korišćena je univarijantna i multivarijantna analiza.

Rezultati: Uključeno je 515 pacijenata (prosečne starosti $54,8 \pm 13,5$ godina, 54,6% muškaraca). Krvarenje je registrovano kod 240 (46,6%) pacijenata. Nezavisni prediktori krvarenja su bili ženski pol ($p = 0,021$, OR = 1,688, IC 95%: [1,081–2,634]), viši ECOG PS ($p = 0,34$, OR = 1,298, IC 95%: [1,021–1,651]), niži broj trombocita ($p < 0,001$, OR = 0,988, IC 95%: [0,983–0,993]) i viši LDH ($p = 0,004$, OR = 1,983, IC 95%: [1,238–3,175]).

Major krvarenje registrovano je kod 37 pacijenata (7,2%). Nezavisni prediktori za major krvarenje su ženski pol ($p = 0,016$, OR = 2,662, IC 95%: [1,197–5,923]), viši INR ($p = 0,002$, OR = 18,377, IC 95%: [2,830–119,317]), i ekspresija CD56 ($p = 0,023$, OR = 2,421, IC 95%: [1,130–5,187]). Krvarenje je bilo uzrok smrti kod 22 (4,3%) pacijenata.

Zaključak: Pacijenti ženskog pola i oni sa CD56 ekspresijom imaju 2,662, odnosno 2,421, puta veću šansu za major krvarenje. Porast INR za 1 povećava šansu za major krvarenjem 18,377 puta. Potrebno je definisati jasne preventivne mere u cilju prevencije major krvarenja kod ove grupe pacijenata.

Ključne reči: akutna mijeloidna leukemija, krvarenje, faktori rizika, predikcija

ABSTRACT

Introduction: Bleeding is one of the major causes of early mortality in patients with acute myeloid leukemia (AML).

Objective: To identify the incidence of bleeding and to define bleeding predictors in AML patients on diagnosis and during the first 30 days.

Methods: A retrospective study including adult non-acute promyelocytic AML patients diagnosed between 2009 and 2023 was conducted. Demographic, initial clinical-laboratory and treatment-related data were collected. Univariate and multivariate analysis were performed.

Results: Among 515 included patients (mean age $54.8 \text{ years} \pm 13.5 \text{ years}$, males 54.6%) bleeding was present in 240 (46.6%). The independent predictors for bleeding, were female sex ($p = 0.021$, OR = 1.688, IC 95%: [1.081–2.634]), higher ECOG PS ($p = 0.34$, OR = 1.298, IC 95%: [1.021–1.651]), lower platelet count ($p < 0.001$, OR = 0.988, IC 95%: [0.983–0.993]) and higher LDH ($p = 0.004$, OR = 1.983, IC 95%: [1.238–3.175]).

Major bleeding was reported in 37 patients (7.2%). The independent predictors for major bleeding, identified through the multivariate analysis were female sex ($p = 0.016$, OR = 2.662, IC 95%: [1.197–5.923]), higher INR ($p = 0.002$, OR = 18.377, IC 95%: [2.830–119.317]), and CD56 expression ($p = 0.023$, OR = 2.421, IC 95%: [1.130–5.187]). The bleeding was cause of the death in 22 (4.3%) patients.

Conclusion: Female patients and patients with CD56 expression had 2.662 and 2.421 times higher chances for major bleeding respectively. INR increment per 1 increases chance for major bleeding 18.377 times. Focused preventive strategies should be developed for patients at high risk for major bleeding.

Keywords: acute myeloid leukemia, bleeding, risk factors, prediction

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RISK FACTORS FOR VENOUS THROMBOEMBOLISM IN ACUTE PROMYELOCYTIC LEUKEMIA

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SAŽETAK

Uvod: Za razliku od krvarenja, nema dovoljno podataka o epidemiologiji i prediktorima venskog tromboembolizma (VTE) kod pacijenata sa akutnom promijelocitnom leukemijom (APL).

Cilj: Identifikovanje incidencije i prediktora za VTE u APL.

Metode: Retrospektivnom studijom, obuhvaćeno je 156 pacijenata sa dijagnozom APL, koji su lečeni u Klinici za hematologiju UKCS od 2006. do 2024. godine, primenom antraciklina i all trans retinoične kiseline. Analizirani su klinički i laboratorijski parametri, kao i efikasnost Al-Ani i Paterno modela za procenu rizika od VTE.

Rezultati: Ukupna stopa VTE iznosila je 18% (28/155). Od toga, 12% je zabeleženo na prezentaciji, 42% tokom indukcije i 46% slučajeva VTE tokom konsolidacije. Najčešća lokalizacija VTE bila je tromboza centralnog venskog katetera u 42% slučajeva, dok je 23% pacijenata imalo tromboze dubokih vena nogu, 4% plućnu tromboemboliju, a 31% ostale lokalizacije. VTE nije bio uzrok nijednog smrtnog ishoda u našoj kohorti. Kao nezavisni faktori rizika za VTE, identifikovani su CD114 ekspresija ($p = 0,005$, OR = 6,4, IC 95% [0,28–9,56]) i odsustvo krvarenja na prezentaciji ($p = 0,013$, OR = 0,086, IC 95% [0,01–0,59]). U našoj analizi, niti Al-Ani niti skor Paterno i saradnika nisu bili prediktivni za VTE.

Zaključak: Ovo je prva analiza u kojoj je pokazano da su CD114 ekspresija i odsustvo krvarenja na prezentaciji korelirali sa nastankom VTE. Za sada nijedan model za procenu rizika nije se pokazao doslednim kod pacijenata sa APL.

Cljučne reči: APL, venski tromboembolizam, rizik

ABSTRACT

Introduction: Data regarding the epidemiology and predictors of venous thromboembolism (VTE) in acute promyelocytic leukemia (APL) stems insufficient.

Objective: to identify the incidence and predictive value of demographic and clinical-laboratory parameters for VTE in APL patients.

Methods: We conducted a retrospective study on 156 adults with APL treated between 2006 and 2024 in Clinic of Hematology UCCS with all-trans retinoic acid and anthracycline. Demographic and clinical-laboratory data related to the VTE were collected. We also analyzed the predictive value of Al-Ani and Paterno risk assessment models (RAM) in our group of patients.

Results: Overall, VTE rate was 18% (28/155). VTE was present at the time of APL diagnosis in 12% cases, while occurring during induction and consolidation cycles in 42% and 46% cases, respectively. Most common thrombosis localization was central venous catheter thrombosis in 42% patients, while 23% had a deep vein thrombosis, 4% pulmonary embolism and other localizations were present in 31% patients. VTE was not the cause of any death. The independent risk factors for VTE were CD114 expression ($p = 0.005$, OR = 6.4, IC 95% [0.28–9.56]) and absence of bleeding on presentation ($p = 0.013$, OR = 0.086, IC 95% [0.01–0.59]). Our analyses showed nor Al-Ani or Paterno RAM were predictive of VTE.

Conclusion: To best of our knowledge, this is the first study that showed a predictive value of CD114 expression and absence of bleeding in patients with APL and thrombosis. Still, there is no adequate RAM to stratify the patients with APL according to the risk of VTE.

Keywords: APL, venous thromboembolism, risk

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FOURNIER'S GANGRENE, A COMPLICATION OF ACUTE MYELOID LEUKEMIA CHEMOTHERAPY – A CASE REPORT

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SAŽETAK

Uvod: Furnijerova gangrena je ozbiljna, često fatalna komplikacija lečenja onkoloških bolesnika, najčešće uzrokovana Gram negativnim bakterijama. S obzirom na sve veću učestalost multirezistentnih sojeva bakterija, ova komplikacija predstavlja veliki izazov lečenja imunokompromitovanih bolesnika.

Prikaz slučaja: Muškarac starosti 52 godine je hospitalizovan na Kliniku za hematologiju radi lečenja akutne mijelomonoblastne leukemije (FLT3 ITD +, 46, XY, ps21). Period postterapijske aplazije, 18. dana od početka reindukcije (Leu 3,02×10⁹/L, ABN 0,84×10⁹/L, Hgb 88 g/L, Trc 39×10⁹/L) se komplikovao pojavom febrilnosti i bolova u desnoj ingvinalnoj regiji sa formiranjem dve manje nekrotične kruste mošnica. Postavljena je sumnja na Furnijerovu gangrenu i izvršena hitna incizija i nekrektomija, uz primenu više linija antibiotske terapije, korigovane spram nalaza antibiograma. Iz inicijalnog brisa rane je izolovana pan-rezistentna *Klebsiella pneumoniae*, a iz kasnijih briseva rane i urinokultura su izolovani *Pseudomonas aeruginosa* i *Acinetobacter baumannii*. Hirurška previjanja su vršena u operacionoj sali, u strogo aseptičnim uslovima, uz redovne konsultacije urologa i plastičnog hirurga. Šezdesetog dana od načinjene incizije je izvršeno zatvaranje rane Tirš graftom uprkos i dalje prisutnoj bakterijskoj kolonizaciji hirurške rane uz adekvatno prihvatanje transplantata. Pet meseci kasnije protočnom citometrijom i biopsijom koštane srži se ne detektuje prisustvo blasta, uz i dalje prisutnu anemiju gradusa 2/3 i trombocitopeniju gradusa 3/4.

Zaključak: Ovaj slučaj prikazuje značaj multidisciplinarnog pristupa lečenju imunokompromitovanih bolesnika.

Ključne reči: nekrotizirajući fasciitis, antibiotska rezistencija, imunokompromitovanost

ABSTRACT

Introduction: Fournier's gangrene is a severe, commonly fatal complication of oncological treatments, most frequently caused by Gram-negative bacteria. Considering the ever-growing number of multidrug-resistant bacteria, this complication presents a significant challenge when treating immunocompromised patients.

Case report: A 52-year-old male patient was hospitalized for acute myeloid leukemia treatment (FLT3 ITD +, 46, XY, ps21). During the posttreatment aplasia, on the 18th day of reinduction (WBC 3.02×10⁹/L, ANC 0.84×10⁹/L, Hgb 88 g/L, Plt 39×10⁹/L) the patient became febrile with pain in his right inguinal region, with two small necrotic crusts on the scrotum. Fournier's gangrene was suspected, and an emergency incision and necrectomy were performed, followed by multiple antibiotic lines guided by an antibiogram. Pandrug-resistant *Klebsiella pneumoniae* was isolated from the initial wound culture, whereas subsequent wound and urine cultures had *Pseudomonas aeruginosa* and *Acinetobacter baumannii* as well. Wound dressings were done in sterile conditions inside the operating room, with constant involvement from urologists and plastic surgeons. The wound was closed on the 60th day after the initial incision with a split-skin graft, despite it still being colonized with bacteria. The transplant was adequately accepted by the patient. Five months later, flow cytometry and a bone marrow biopsy were performed, and no blasts were detected, whereas grade 2/3 anemia and grade 3/4 thrombocytopenia persist.

Conclusion: This case presents the importance of a multidisciplinary approach when treating immunocompromised patients.

Keywords: necrotizing fasciitis, microbial drug resistance, immunocompromised

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PRIKAZ PACIJENTKINJE SA AKUTNOM PROMIJELOCITNOM LEUKEMIJOM I ENCEFALITISOM – DIFERENCIJALNA DIJAGNOZA IZMEĐU INFEKTIVNIH KOMPLIKACIJA I DIFERENCIJALNOG SINDROMA

PRESENTATION OF A PATIENT WITH ACUTE PROMYELOCYTIC LEUKEMIA AND ENCEPHALITIS – DIFFERENTIAL DIAGNOSIS BETWEEN INFECTIOUS COMPLICATIONS AND DIFFERENTIATION SYNDROME

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SAŽETAK

Uvod: Akutna promijelocitna leukemija (APL) je u viskom procentu izlečiv oblik leukemije koju karakteriste predominacija promijelocita u koštanoj srži. Rinocerebralna mukormukoza i HSV encefalitis su retke komplikacije sa visokom stopom mortaliteta kod imunokompromitovanih pacijenata.

Prikaz slučaja: Kod pacijentkinje ženskog pola, 71 godina, postavljena je dijagnoza APL, visokog stepena rizika. Započeto je lečenje indukcijom hemioterapijom PETHEMA LPA 2012. Zbog pada SpO₂ na 80% ukinuta je ATRA zbog sumnje na diferencijacioni sindrom i primenjena terapija dexametasonom. MDCT toraksa: U posteriornom segmentu gornjeg režnja desno promene po tipu „tree in bud“. Serologija na gljive je bila negativna. Zbog sumnje na invazivnu mukormukoza započeto lečenje liposomalnim amfotericinom B (L-AmB) 3 mg/kg i.v. Na D19 primećena je ptoza desnog kapka i somnolencija. NMR endokranijuma je ukazao na pansinusitis i encefalitis, tj na moguću rinocerebralnu mukormukoza, te je eskalirana doza L-AmB na 5 mg/kg i.v. PCR na HSV1 pozitivan. Lečena je antibioticima, antivirusima, vazopresorom, oksigenoterapijom i antiedematoznom terapijom. Pored svih primenjenih mera terapije nastupio je smrtni ishod.

Zaključak: Hematološki maligniteti i imunosupresivna terapije su predisponirajući faktori za nastanak različitih infektivnih komplikacija. Primena različitih imaging metoda, kao i serološke dijagnostike su ključni u postavljanju dijagnoze i pravovremenog započinjanja lečenja. Efikasnu antifungalnu terapiju treba primeniti što je pre moguće, a lek izbora za lečenje rinocerebralne mukormukoze je L-AmB.

Ključne reči: akutna promijelocitna leukemija, rinocerebralna mukormukoza, encefalitis

ABSTRACT

Introduction: Acute promyelocytic leukemia (APL) is a highly curable form of leukemia characterized by the predominance of promyelocytes in the bone marrow. Rhinocerebral mucormucosis and HSV encephalitis are rare complications with a high mortality rate in immunocompromised patients.

Case report: A 71-year-old female patient was diagnosed with high-risk APL. Treatment started with induction chemotherapy PETHEMA LPA 2012. Due to drop of SpO₂ to 80%, ATRA was discontinued due to suspicion of differentiation syndrome and dexamethasone therapy was administered. MDCT of the thorax: In the posterior segment of the upper lobe on the right, „tree in bud“ type changes. Fungal serology was negative. Due to suspicion of invasive mucormucosis, treatment with liposomal amphotericin B (L-AmB) 3 mg/kg i.v. was started. On day 19, ptosis of the right eyelid and somnolence were observed. NMR of the endocranium indicated pansinusitis and encephalitis, i.e. possible rhinocerebral mucormucosis, and the dose of L-AmB was escalated to 5 mg/kg i.v. PCR for HSV1 positive. She was treated with antibiotics, antivirals, vasopressor, oxygen therapy and anti-edematous therapy. In addition to all applied therapeutic measures, a fatal outcome occurred.

Conclusions: Hematological malignancies and immunosuppressive therapies are predisposing factors for the occurrence of various infectious complications. Application of various imaging methods, as well as serological diagnostics, are crucial in establishing a diagnosis and timely initiation of treatment. Effective antifungal therapy should be administered as soon as possible, and L-AmB is the drug of choice for the treatment of rhinocerebral mucormucosis.

Keywords: acute promyelocytic leukemia, rhinocerebral mucormucosis, encephalitis

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PREDICTORS OF EARLY DEATH IN ACUTE PROMYELOCYTIC LEUKEMIA AND SCORS FOR RISK STRATIFICATION

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SAŽETAK

Uvod: Rana smrt (Early Death, ED) predstavlja i dalje najveću prepreku za postizanje uspeha u lečenju pacijenata sa akutnom promijelocitnom leukemijom (APL). Nedavno je napravljen novi ED skor, kojim se pacijenti sa APL stratifikuju u tri grupe rizika (nizak, visok, veoma visok).

Cilj: Procena efikasnosti ED skora u našoj kohorti.

Metode: Retrospektivnom studijom, obuhvaćeno je 156 pacijenata sa dijagnozom APL, koji su lečeni u Klinici za hematologiju UKCS od 2006. do 2024. godine, primenom antraciklina i all trans retinoične kiseline. Analizirani su klinički i laboratorijski parametri, kao i efikasnost Sanz i novog ED skora za procenu rizika od ED.

Rezultati: Stopa ED iznosila je 26% (40/156). Najčešći uzrok smrti bila je hemoragija (15/40, 37,5%). Prema multivarijantnoj analizi, pacijenti sa višim ECOG PS (OR 3,17; 95% CI 1,91–5,26, $p < 0,001$) i nižom vrednošću aPTT (OR = 0,834; 95% CI 0,71–0,98, $p = 0,027$) imali su veći rizik od ED. Na osnovu ED skora, 43% pacijenata je bilo u grupi niskog, 44% u grupi visokog i 13% u grupi veoma visokog rizika. Stopa ED iznosila je: 12% za nizak, 33% za visok i 45% za veoma visok rizik. U našoj analizi, oba skora (ED skor i Sanz skor) su podjednako efikasna u predikciji ED sa AUC vrednošću od 0,67 (95% CI 0,57–0,77) vs. 0,69 (95% CI 0,60–0,78).

Zaključak: Novi ED skor podjednako je efikasan kao i Sanz skor za procenu rizika od ED. Pokazano je da pacijenti sa višim ECOG PS i nižim aPTT na prezentaciji imaju veći rizik od ED.

Ključne reči: APL, rana smrt, prediktor

ABSTRACT

Introduction: Early death (ED) presents the major impediment in acute promyelocytic leukemia (APL) treatment. Recently, a novel score has been made in order to stratify patients into three groups (low, high, very high) according to the risk of ED.

Objective: Evaluation of efficacy of new ED score in our cohort.

Methods: We conducted a retrospective study on 156 adults with APL treated between 2006 and 2024 in Clinic for Hematology UCCS with all-trans retinoic acid and anthracycline. Demographic and clinical-laboratory data were collected. We analyzed the predictive value of Sanz and new ED risk score.

Results: ED rate was 26% (40/156) with hemorrhage as a most common cause (15/40, 37.5%). According to multivariate analysis, patients with higher ECOG PS (OR 3.17; 95% CI 1.91–5.26, $p < 0.001$) and lower APTT (OR = 0.834; 95% CI 0.71–0.98, $p = 0.027$) had significantly higher risk of ED. According to ED score, 43% patients were in low-, 44% in high- and 13% in very high risk group. ED rates for each groups were 12%, 33% and 45%, respectively. Both scores (ED score and Sanz score) were equally effective in predicting risk of ED with the AUC of 0.67 (95% CI 0.57–0.77) vs. 0.69 (95% CI 0.60–0.78).

Conclusion: New ED score is equally effective in predicting the risk of ED as the Sanz risk score. Patients with higher ECOG PS and shorter APTT have increased risk of ED, but this results need to be confirmed in larger study.

Keywords: APL, early death, predictor

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KOMBINACIJA AZACITIDINA I VENETOKLAKSA U LEČENJU NOVODIJAGNOSTIKOVANIH I RELAPS/REFRAKTERNIH BOLESNIKA SA AKUTNOM MIJELOIDNOM LEUKEMIJOM – ISKUSTVO JEDNOG CENTRA

THE COMBINATION OF AZACITIDINE WITH VENETOCLAX IN THE TREATMENT OF NEWLY DIAGNOSED AND RELAPSED/REFRACTORY PATIENTS WITH ACUTE MYELOID LEUKEMIA – A SINGLE CENTER EXPERIENCE

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SAŽETAK

Uvod: Lečenje obolelih od akutne mijeloidne leukemije koji nisu kandidati za intenzivnu hemioterapiju kao i relaps/refrakternih bolesnika je povezano sa lošom prognozom i lošim ukupnim preživljavanjem. Međutim, primena hipometilisućih agenasa u kombinaciji sa bcl2 inhibitorima u lečenju pomenute dve grupe bolesnika je dovela do poboljšanja ishoda lečenja.

Cilj: Prikazati rezultate lečenja obolelih od akutne mijeloidne leukemije kombinacijom azacitidina i venetoclaxa.

Metode: Studijom preseka obuhvaćeni su svi bolesnici koji su do sada lečeni na Klinici za hematologiju kombinacijom azacitidina i venetoklaksa, bilo da je u pitanju bila prva linija terapije ili u relaps/refrakternoj AML.

Rezultati: Na Klinici za hematologiju UKCV je do sada lečeno ukupno 8 bolesnika kombinacijom azacitidina i venetoklaksa, u periodu od novembra meseca 2023. godine do juna 2024. godine. Kod tri bolesnika radilo se o prvoj liniji terapije, kod dvoje je terapija primenjena za lečenje ranog relapsa, odnosno terapije održavanja nakon alogene transplantacije matičnih ćelija, dok je kod preostala tri bolesnika terapija primenjena nakon izostanka odgovora na standardne salvage hemioterapijske protokole. Tromesečna stopa preživljavanja bez bolesti je iznosila 37,5%. Kod dva bolesnika zabeležene su infektivne komplikacije koje su bile uzrok smrtnog ishoda, dok je kod tri bolesnika potvrđen relaps bolesti nakon drugog ciklusa terapije.

Zaključak: Kombinacija azacitidina i venetoklaksa pruža jednu dodatnu važnu opciju u lečenju obolelih od akutne mijeloidne leukemije, sa neophodnošću pažljivog praćenja ovih bolesnika zbog potencijalnih komplikacija, posebno mijelotoksičnog efekta i infektivnih događaja.

Ključne reči: azacitidin, venetoklaks, preživljavanje

ABSTRACT

Introduction: Treating patients with acute myeloid leukemia who are not eligible for intense chemotherapy as well as relapsed/refractory patients is associated with poor prognosis. However, since the introduction of hypomethylating agents in combination with bcl2 inhibitors treatment outcomes have improved.

Objective: To evaluate the efficacy of azacitidine and venetoclax treatment in patients with acute myeloid leukemia.

Methods: A cross-sectional study included all patients who have been treated at the Clinic of Hematology with a combination of azacitidine and venetoclax, whether the therapy was a first line treatment or not.

Results: At our Clinic of hematology, a total of 8 patients have been treated with a combination of azacitidine and venetoclax, from November 2023 till June 2024. In three patients it was given as a first line treatment, in two patients the therapy was applied for the treatment of early relapse and as a maintenance therapy after allogeneic stem cell transplantation, while in the remaining three patients the therapy was applied after the lack of response to standard salvage chemotherapy protocols. The three-month progression-free survival rate was 37.5%. Infectious complications were recorded in two patients, which were also the cause of death, while in three patients relapse of the disease was confirmed after the second cycle of therapy.

Conclusion: The combination of azacitidine and venetoclax provides an additional important option in the treatment of patients with acute myeloid leukemia, with the necessity of careful monitoring due to potential complications such as myelotoxicity and infectious events.

Keywords: azacitidine, venetoclax, survival

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ENASIDENIB U KOMBINACIJI SA AZACITIDINOM I VENETOKLAKSOM U LEČENJU RELAPS/REFRAKTERNE IDH2^{mut} AKUTNE MIJELOIDNE LEUKEMIJE – PRIKAZ SLUČAJA

ENASIDENIB, AZACITIDINE AND VENETOCLAX IN THE TREATMENT OF RELAPSED/REFRACTORY IDH2^{mut} ACUTE MYELOID LEUKEMIA – A CASE REPORT

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SAŽETAK

Uvod: Enasidenib (ENA) je prvi u klasi oralni IDH2 inhibitor registrovan za lečenje relaps/refrakterne (R/R) IDH2^{mut} akutne mijeloidne leukemije (AML). Iako je ENA registrovan kao monoterapija, preliminarni rezultati kombinovane terapije sa azacitidinom (AZA) i venetoklaksom (VEN) su obećavajući.

Cilj: Prikazati lečenje R/R IDH2^{mut} AML primenom trojne kombinacije (ENA/AZA/VEN).

Prikaz slučaja: Bolesnik je muškarac, u momentu dijagnoze 36 godina. Dijagnoza bolesti (AML sa znacima displazije, normalan kariogram, CD56+, FLT3^{neg}) je postavljena u januaru 2019. godine. Nakon dve indukcije (3+7 i ICE), nije postignuta kompletna remisija. Na primenjenu *salvage* terapiju (FLAG) ulazi u kompletnu remisiju. Nakon dve konsolidacione terapije je u avgustu 2019. transplantiran (alogeno transplantacija matičnih ćelija hematopoeze od HLA identičnog nesrodnog donora). Do relapsa bolesti dolazi u januaru 2024. kada je urađena i dopunska molekularna dijagnostika, koja je otkrila prisustvo ASXL1 mutacije (21% VAF), kao i IDH2 mutacije (19% VAF). NGS analiza (mijeloidni panel, NovaSeq6000, Illumina®) aspirata koštane srži je urađena u Medicover Diagnostics u Nemačkoj. Lečenje je nastavljeno intenzivnom hemioterapijom (FLA, odnosno MEC), nakon čega se konstatuje rezistencija (progresija blasta u koštanoj srži sa inicijalnih 40% na 75% nakon dve terapije). Dalje lečenje je nastavljeno primenom ENA/AZA/VEN trojne kombinacije. Prvi ciklus (28 dana) je započet sa AZA (75 mg/m² sc 7 dana) i VEN (100 mg prvi dan, pa 200 mg kontinuirano), dok je ENA dodat od 15. dana u dozi 100 mg/dan kontinuirano. Terapiju je dobro podneo, nije bilo znakova diferencijacionog sindroma. Nakon prvog ciklusa je postignut parcijalni odgovor (redukcija blasta na oko 10%), dok je nakon II ciklusa terapije postignuta kompletna morfološka remisija (protočnom citometrijom 0,7% blasta). U toku je priprema za sekundarnu alogenu transplantaciju.

Zaključak: R/R AML, posebno nakon alogene transplantacije, predstavlja izazov u lečenju. Primena ciljane terapije u kombinaciji sa inovativnim lekovima, pokazuje efikasnost uz malu toksičnost terapije i može poslužiti kao *bridge* do sekundarne transplantacije.

Ključne reči: enasidenib, IDH2, AML, relaps, R/R

ABSTRACT

Introduction: Enasidenib (ENA) is a first-in-class oral IDH2 inhibitor approved for the treatment of relapsed/refractory acute myeloid leukemia (AML) with IDH2 mutation. Although ENA is registered as a monotherapy, preliminary results from combination therapy with azacitidine (AZA) and venetoclax (VEN) are promising.

Objective: To report on the treatment of R/R IDH2^{mut} AML using a triple combination (ENA/AZA/VEN).

Case report: In January 2019, a 36-year-old male was diagnosed with AML with dysplasia (normal karyogram, CD56+, and FLT3^{neg}). Despite two induction therapies (3+7 and ICE), full remission was not attained. Following the use of salvage therapy (FLAG), the patient achieved complete remission. After two consolidation therapies, he underwent allogeneic hematopoietic stem cell transplantation from an HLA-identical unrelated donor in August 2019. In January 2024, the disease relapsed, prompting additional molecular diagnostics. The presence of ASXL1 (21% VAF) and IDH2 mutations (19% VAF) was revealed. NGS analysis on bone marrow aspirate was performed at Medicover Diagnostics in Germany, employing the myeloid panel, NovaSeq6000, and Illumina® platform. Treatment was continued with intensive chemotherapy (FLA and MEC). Resistance was established, evidenced by the progression of blast counts in the bone marrow from initial 40% to 75% after two treatments. Further management involved a triple combination of ENA/AZA/VEN. The first 28-day cycle began with AZA (75 mg/m² subcutaneously for 7 days) and VEN (100 mg on the first day, then 200 mg daily). ENA was introduced from the 15th day at a dose of 100 mg/day. The patient responded well to the treatment, with no signs of differentiation syndrome. The initial treatment cycle led to a substantial reduction in blast counts (10%). Following the second cycle, a complete remission was achieved, as evidenced by a flow cytometry report (0.7% of blasts). Preparation for secondary allogeneic transplantation is currently underway.

Conclusion: R/R AML, particularly after allogeneic transplantation, presents significant treatment challenge. The use of targeted therapies alongside innovative drugs demonstrates effectiveness with minimal toxicity, offering a viable pathway to secondary transplantation.

Keywords: enasidenib, IDH2, AML, relaps, R/R

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HRONIČNA LIMFOCITNA LEUKEMIJA I LEUKEMIJA VLASASTIH ČELIJA

CHRONIC LYMPHOCYTIC LEUKEMIA AND HAIRY CELL LEUKEMIA

EVALUATION OF THE EFFICACY AND SIGNIFICANCE OF THE IMMUNOCHEMOTHERAPY PROTOCOL OBINUTUZUMAB-CHLORAMBUCIL IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA AND A HIGH COMORBIDITY INDEX

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SAŽETAK

Uvod: Hronična limfocitna leukemija (HLL) karakteriše se proliferacijom monoklonskih B-limfocita sa koekspresijom CD5 i CD23. U klinički heterogenom momentu progresije, izbor terapije zavisi od molekularno-prognostičkog profila, stadijuma bolesti, starosti pacijenta i komorbiditeta. Ciljana terapija menja ranije pristupe, dok imunoheмотerapija ostaje značajna za određene pacijente.

Cilj: Analiza prediktivnih faktora relapsa i mortaliteta kod prethodno nelečenih pacijenata sa HLL i visokim komorbiditetnim indeksom (CIRS), kod kojih je primenjen obinutuzumab i hlorambucil (O-Clb).

Metode: Retrospektivna kohortna studija obuhvatila je 37 pacijenata sa HLL i CIRS > 6, lečenih protokolom O-Clb u prvoj liniji, od novembra 2018. do februara 2024. na Klinici za hematologiju UKCS. Korišćene su deskriptivne statističke metode, Kaplan-Majer analiza za preživljavanje, a Cox regresiona analiza za prediktore mortaliteta, sa alfa nivoom značajnosti 0,05 u SPSS 25.

Rezultati: Od 37 pacijenata, 9 (24,3%) je doživelo relaps. Pacijenti sa relapsom češće su imali inicijalni RAI stadijum 0 ($p = 0,042$). Smrtnost je bila 21,6%, sa medijanom vremena do smrti od 17 meseci. Pacijenti sa smrtnim ishodom su pokazali značajno niže vrednosti hemoglobina ($p = 0,010$) i albumina ($p = 0,029$). Hemoglobin < 120/110 ($p = 0,016$), albumin < 40 ($p = 0,010$) i LDH ≥ 435 ($p = 0,024$) su bili značajni faktori rizika za mortalitet u univarijantnom Cox modelu. Albumin < 40 ($p = 0,010$) je bio najznačajniji prediktor u multivarijantnoj Cox regresiji.

Zaključak: Kod pacijenata sa HLL i visokim komorbiditetnim indeksom, primena O-Clb pokazuje značajne terapijske efekte. Ključni prediktori relapsa i mortaliteta uključuju inicijalni RAI stadijum, vrednosti hemoglobina, albumina i LDH, sa albuminima < 40 g/L kao značajnim nezavisnim faktorom rizika za mortalitet.

Ključne reči: hronična limfocitna leukemija, obinutuzumab, hlorambucil, komorbiditetni indeks

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ABSTRACT

Introduction: Chronic lymphocytic leukemia (CLL) is characterized by the proliferation of monoclonal B-lymphocytes expressing CD5 and CD23 antigens, exhibiting clinical heterogeneity. Treatment decisions rely on molecular-prognostic profiles, disease stage, age, and comorbidities. While targeted therapies have transformed treatment, immunochemotherapy remains crucial for specific cohorts.

Objective: To evaluate the efficacy of obinutuzumab plus chlorambucil in immunochemotherapy and analyze predictive factors for relapse and mortality, for treatment-naïve CLL patients with a high comorbidity index.

Methods: A retrospective cohort study included 37 CLL patients with a comorbidity index > 6, treated with obinutuzumab and chlorambucil as first-line therapy from November 2018 to February 2024 at the Hematology Clinic of the University Clinical Center of Serbia. Descriptive statistics and Kaplan-Meier analysis assessed survival, while Cox regression analyzed mortality predictors using SPSS 25 (significance level $\alpha = 0.05$).

Results: Among 37 patients, 9 (24.3%) experienced relapse, notably associated with initial RAI stage 0 ($p = 0.042$). Mortality rate was 21.6%, median survival 17 months. Patients with fatal outcomes had significantly lower hemoglobin ($p = 0.010$) and albumin levels ($p = 0.029$). Hemoglobin < 120/110 ($p = 0.016$), albumin < 40 ($p = 0.010$), and LDH ≥ 435 ($p = 0.024$) were mortality risk factors in univariate Cox regression. In multivariate analysis, albumin < 40 ($p = 0.010$) was the strongest predictor.

Conclusion: In CLL patients with high comorbidity index, obinutuzumab plus chlorambucil immunochemotherapy demonstrates significant efficacy. Key prognostic factors for relapse and mortality include initial RAI stage, hemoglobin, albumin, and LDH levels, with albumin < 40 g/L as a critical independent mortality risk factor.

Keywords: chronic lymphocytic leukemia, obinutuzumab, chlorambucil, comorbidity index

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LEUKEMIA CUTIS AS A MANIFESTATION OF CHRONIC LYMPHOCYTIC LEUKEMIA – A CASE REPORT

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SAŽETAK

Uvod: Infiltracija kože kod hronične limfocitne leukemije (CLL) je retka pojava i javlja se kod 4–20% pacijenata. Specifične lezije kože uključuju leukemiju kože (leukemia cutis) i Rihterov sindrom. Leukemija kože se definiše kao leukemijska infiltracija epidermisa, dermisa i potkožnog tkiva.

Prikaz slučaja: Prikazujemo 59-godišnjeg pacijenta sa dijagnozom CLL/SLL postavljenom biopsijom limfnog čvora na vratu u aprilu 2021.g. sa tipičnom imunofenotipizacijom limfocita periferne krvi (CLL skor 5). Pacijent je praćen do decembra 2022.g. kada je urađena tonsilektomija zbog uvećanog i hipertrofičnog levog krajnika. Histopatološki nalaz potvrdio je infiltraciju (imunohistohemijske analize: CD20+, PAX5+, BCL-2+, CD23+, CD5+, CD3-, BCL-6-, CD10-, SOX-11-, Cyclin D1-, IgD-, CD138-, kappa-, lambda-, c-MYC, MUM-1-, Ki-67+ u oko 20% tumorskih ćelija). Biopsija koštane srži pokazala je oko 80% infiltraciju malim limfocitima. Zbog induriranih promena i nodulusa lividno-eritematozne boje na koži lica u predelu korena nosa i kapilicijuma urađena je biopsija kože. Histopatološki nalaz odgovarao je infiltraciji kože kod CLL. Fluorescentna in situ hibridizacija (FISH) otkrila je deleciju 13q14 regiona u 30% analiziranih nukleusa. Delecija u RB1 (retinoblastom) genu otkrivena je sekvenciranjem gena, a mutacija T53 nije detektovana. Pacijent je lečen imunohemioterapijom (RFC protokol – rituksimab-ciklofosamid-fludarabin) sa povoljnim efektom i nakon 5. ciklusa promene na koži su se povukle u potpunosti.

Zaključak: U većini slučajeva kožne lezije kod CLL se javljaju nakon postavljanja dijagnoze, a najčešće lokalizacije su na koži glave i vrata. Kod našeg pacijenta se radilo o difuznom tipu infiltracije. Prognostički značaj infiltracije kože nije poznat.

Ključne reči: hronična limfocitna leukemija, leukemija kože, infiltracija

ABSTRACT

Introduction: Skin infiltration in chronic lymphocytic leukemia (CLL) is a rare phenomenon and occurs in 4–20% of patients. Specific skin lesions include leukemia cutis and Richter’s syndrome. Skin leukemia is defined as leukemic infiltration of the epidermis, dermis and subcutaneous tissue.

Case report: We present a 59-year-old patient with a diagnosis of CLL/SLL confirmed by a neck lymph node biopsy in April 2021. with typical immunophenotyping of peripheral blood lymphocytes (CLL score 5). The patient was monitored until December 2022. when a tonsillectomy was performed due to a hypertrophic left tonsil. Histopathological findings confirmed infiltration (immunohistochemical analysis: CD20+, PAX5+, BCL-2+, CD23+, CD5+, CD3-, BCL-6-, CD10-, SOX-11-, Cyclin D1-, IgD-, CD138-, kappa-, lambda-, c-MYC, MUM-1-, Ki-67+ in about 20% of tumor cells). Bone marrow biopsy showed 80% infiltration by small lymphocytes. Due to indurated changes and nodules of livid-erythematous color on the skin of the face in the area of the root of the nose and the hairline, a skin biopsy was performed. Histopathological findings corresponded to skin infiltration in CLL. Fluorescence in situ hybridization revealed the deletion of the 13q14 region in 30% of the analyzed nuclei. A deletion in the RB1 gene was detected by gene sequencing, and the T53 mutation was not detected. The patient was treated with immunochemotherapy (RFC protocol – rituximab, cyclophosphamide, fludarabine) with a favorable effect and after the 5th cycle, the changes on the skin disappeared completely.

Conclusion: In most cases, skin lesions in CLL appear after diagnosis, and the most common localizations are on the skin of the head and neck. The prognostic significance of skin infiltration is not known.

Keywords: chronic lymphocytic leukemia, skin leukemia, infiltration

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HODGKIN TRANSFORMATION OF CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA

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SAŽETAK

Uvod: Hronična limfocitna leukemija (HLL)/limfom malih limfocita se u retkim slučajevima može transformisati u Hočkinov limfom, a u literaturi je do sada opisano oko sto ovakvih slučajeva.

Cilj: Prikazujemo bolesnika sa Hočkinovom varijantom Rihterove transformacije.

Prikaz slučaja: Godinu dana nakon početka kontrolnog praćenja, kod 60-godišnjeg muškarca sa HLL došlo je do razvoja B simptoma, generalizovane limfadenopatije i splenomegalije. Posle početnog određivanja stadijuma bolesti (Binet B/Rai 3), započeto je lečenje prema protokolu fludarabin, ciklofosfamid, rituksimab (FCR). Nakon trećeg ciklusa lečenja i dalje se održavala i postajala bolna, desnostrana pazušna limfadenopatija, dok su se dimenzije preostalih, bolešću zahvaćenih organa, smanjile. Po okončanju poslednjeg, šestog ciklusa FCR terapije, bolna desnostrana pazušna limfadenopatija se održavala (iako se delimično smanjila u veličini), sa razvojem lokalnog crvenila i otoka. Biopsijom zaostalog pazušnog nodusa dokazana je transformacija bolesti u Hočkinov limfom. Nakon određivanja stadijuma bolesti na osnovu nalaza multislajsne kompjuterizovane tomografije (IV E klinički stadijum) i procene prognoze (nepovoljna prognoza), odlučeno je da se lečenje nastavi prema protokolu doksorubicin, vinblastin, dakarbazin (AVD). Bolesnik je preminuo dva meseca nakon potvrde dijagnoze Hočkinove transformacije (HT), u toku sprovođenja prvog AVD.

Zaključak: Mada je HLL sporo progresivna maligna bolest, u retkim slučajevima sa HT prognoza je nepovoljna. Dostupne terapijske mogućnosti daju suboptimalne rezultate, mada bi u skorijoj budućnosti inovativne imunološke terapije mogle izmeniti tok lečenja bolesnika sa HT.

Ključne reči: Rihterova transformacija, hronična limfocitna leukemija, limfom malih limfocita, Hočkinov limfom

ABSTRACT

Introduction: In rare cases, chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma may transform into Hodgkin lymphoma, with about a hundred cases reported in the literature so far.

Objective: We present a case of the Hodgkin variant of Richter transformation.

Case report: After a one-year watch and wait period, a 60-year-old male with CLL developed B symptoms, generalized lymphadenopathy, and splenomegaly. Upon initial staging (Binet B/Rai 3), he was started on fludarabine, cyclophosphamide, and rituximab (FCR) regimen. After the third cycle of treatment, the right-sided axillary lymphadenopathy persisted and became painful, while the dimensions of the remaining organs affected by the disease decreased. Upon the finalization of the final sixth FCR cycle, the painful right-sided axillary lymphadenopathy persisted (though partially decreasing in size), with the development of local redness and swelling. A biopsy of the residual axillary node was performed, which revealed disease transformation into Hodgkin lymphoma. Upon multislice computed tomography-based staging (IV E clinical stage) and prognostic assessment (unfavorable prognosis), it was decided that the treatment be continued with doxorubicin, vinblastine, dacarbazine (AVD) regimen. The presented patient died two months after the diagnosis of Hodgkin transformation (HT) was established during the initial cycle of AVD.

Conclusion: Although CLL is an indolent malignancy, in rare cases of HT, the prognosis is largely dismal. The available treatment strategies demonstrate suboptimal results, although novel immunotherapies may change the landscape of HT therapy in the near future.

Keywords: Richter transformation, chronic lymphocytic leukemia, small lymphocytic lymphoma, Hodgkin lymphoma

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MULTIPLE SECONDARY MALIGNANCIES IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA – A CASE REPORT

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SAŽETAK

Uvod: Rizik pojave drugih primarnih maligniteta kod obolelih od hronične limfocitne leukemije (HLL) je povećan zbog poremećenog imunološkog nadzora u sklopu HLL, ali i kao moguća posledica primenjene terapije.

Prikaz slučaja: Pacijentkinji staroj 65 godina HLL je otkrivena u asimptomatskom B stadijumu. Zbog kompresivnih i konstitucionalnih simptoma, dve godine kasnije, lečenjem po FCR protokolu postignut je parcijalni odgovor koji je trajao manje od godinu dana. Dve godine kasnije u terapiju relaps/rezistentne HLL, kao 5. terapijska linija, posle CHOP, Hlorambucil+Leukeran i visokih doza metilprednizolona je uveden ibrutinib. Sedam godina od dijagnoze, a pet od započinjanja lečenja, dijagnostikovao je duktalni invazivni karcinom dojke. Urađena je poštena operacija i uveden tamoksifen uz nastavak terapije ibrutinibom. Dve godine kasnije, dijagnostikovani su papilarni karcinom štitaste žlezde i skvamocelularni karcinom kože, bez udaljenih metastaza, lečeni hirurški. Posle godinu dana, zbog lokalnog recidiva karcinoma dojke je urađena mastektomija, uveden eksemestan i indikovana radioterapija. Ibrutinib je obustavljan samo u vreme planiranih invazivnih procedura. Ekstirpirani limfni čvorovi aksilarne regije, prilikom mastektomije, su bili infiltrisani ćelijama HLL. Nije bilo drugih tegoba vezanih za HLL, ima normalnu krvnu sliku, bez hepatosplenomegalije i limfadenomegalije.

Zaključak: Studije pokazuju da alkilirajući agensi, purinski analozi i imunosupresivna terapija značajno povećavaju rizik od sekundarnih maligniteta (SM). Upotreba BTK inhibitora, prema studiji E1912, pokazuje veću, ali statistički nesigificantnu, incidencu SM, dok druge studije pokazuju manju incidencu. Pažljivo praćenje obolelih od HLL u cilju ranog otkrivanja SM je neophodno nezavisno od vrste primenjene terapije.

Ključne reči: hronična b-limfocitna leukemija, neoplazma, druga primarna, fludarabin, ibrutinib, imunosupresivni agensi

ABSTRACT

Introduction: Patients with chronic lymphocytic leukemia (CLL) have an increased risk of developing other primary malignancies due to impaired immune surveillance associated with CLL and potential treatment-related effects.

Case report: A 65-year-old female was diagnosed with asymptomatic B-stage CLL. Two years later, due to compressive and constitutional symptoms, treatment with the FCR protocol resulted in a partial response lasting less than a year. For relapsed/refractory CLL, as the 5th line of therapy, following CHOP, Chlorambucil+Leukeran, and high-dose methylprednisolone, ibrutinib was introduced. Seven years post-diagnosis and five years after starting treatment, the patient was diagnosed with invasive ductal carcinoma of the breast. She underwent breast-conserving surgery and started tamoxifen while continuing ibrutinib. Two years later, she was diagnosed with papillary thyroid carcinoma and squamous cell carcinoma of the skin, treated surgically without distant metastases. The following year, due to local recurrence of breast cancer, she had a mastectomy, started exemestane, and radiotherapy was indicated. Ibrutinib was paused only during planned invasive procedures, completed without complications. The patient remained asymptomatic for CLL, with a normal blood count and no hepatosplenomegaly or lymphadenomegaly. However, pathohistological examination of lymph nodes removed during mastectomy showed infiltration by CLL cells.

Conclusion: Studies show that alkylating agents, purine analogs, and immunosuppressive therapy significantly increase the risk of secondary malignancies (SM). The E1912 study suggests a higher but statistically insignificant incidence of SM with BTK inhibitors, while other studies indicate a lower incidence. Careful monitoring of CLL patients for early SM detection is essential, regardless of therapy type.

Keywords: chronic b-lymphocytic leukemia, neoplasm, second primary, fludarabine, ibrutinib, immunosuppressive agent

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CHALLENGES IN TREATMENT OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKAEMIA – CLINICAL CASE

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SAŽETAK

Uvod: Lečenje pacijenata sa hroničnom limfocitnom leukemijom (HLL) prime-nom ciljane terapije je pod uticajem komorbiditeta, konkomitatne terapije i tok-sičnosti lekova.

Prikaz slučaja: Kod pacijentkinje stare 62 godine nakon uočene limfocitoze i periferne limfadenopatije do 3cm postavljena je dijagnoza HLL u maju 2012. Am-bulantno je praćena do aprila 2013. kada je zbog progresije bolesti sprovedeno lečenje primenom 6 ciklusa fludarabina i ciklofosfamida uz efekat kompletne remisije. U septembru 2019. pored B simptoma registrovana je leukocitoza (Le 213,4x10⁹/L) i generalizovana limfadenopatija. Lečena primenom imunoterapije, ali zbog povrede kičme lečenje obustavljeno nakon 2 ciklusa. U martu 2022. uo-ćena leukocitoza (Le 221,6x10⁹/L). Fluorescentna in situ hibridizacija ukazala je na deleciju 13q i 17p. Otpočeto je sa primenom ibrutiniba u avgustu 2022., inicijalno bez neželjenih efekata. Zbog bolova u grudima, dispneje i izrazitog zamaranja u decembru 2022. urađen je ultrazvuk srca kojim je otkrivena hipokinezija i uve-ćanje leve komore uz redukciju ejekcione frakcije na 35%. Zbog kardiotsično-sti (srčana insuficijencija gradus 3) obustavljen je ibrutinib. U julu 2023. tokom hospitalizacije radi uvođenja venetoklaks otkrivena je tumefakcija 2,5 cm u levoj dojci. Biopsijom je potvrđena dijagnoza duktalnog invazivnog karcinoma, a nakon tumorektomije primenjivan je letrozol. Ramp-up venetoklaks je otpo-čet u novembru 2023. (Le 177x10⁹/L, Hb 105 g/L, Tr 65x10⁹/L; limfadenopatija do 3 cm; splenomegalija 6cm pod rebarnim lukom), a kompletiran u decembru, uz zadovoljavajući terapijski odgovor (Le 3.63x10⁹/L, Hb 97 g/L, Tr 261x10⁹/L, limfa-denopatija do 1,5 cm).

Zaključak: Tokom perioda praćenja i lečenja pacijenata sa HLL potrebno je ree-valuirati pojavu maligniteta, toksičnosti lekova i komorbiditeta.

Ključne reči: HLL, ibrutinib, venetoklaks, kardiotsičnost, malignitet

ABSTRACT

Introduction: Treatment of patients with chronic lymphocytic leukaemia (CLL) with targeted therapy is altered by comorbidities, concomitant medication and drug toxicity.

Case report: A 62-year-old female without comorbidities was diagnosed with CLL in May 2012, after presenting with lymphocytosis and peripheral lymphadenopathy up to 3cm. Watch-and-wait approach followed diagnosis. Disease progression in April 2013 led to 6 cycles of fludarabine and cyclophosphamide achieving complete remission. In September 2019 B symptoms, leucocytosis (Le 213.4x10⁹/L) and generalised lymphadenopathy reappeared. Immunochemotherapy was limited to 2 cycles due to spinal injury (L2 fracture). Relapse appeared in March 2022 (Le 221.6x10⁹/L). Fluorescence in situ hybridisation analysis confirmed deletion of 13q and 17p. Ibrutinib was started in August 2022 without initial side effects. In December 2022 echocardiography due to chest pain, dyspnoea and extreme fatigue revealed left ventricle enlargement, hypokinesia, and ejection fraction reduction (35%). Due to cardiotoxicity (heart failure grade 3) ibrutinib was discontinued. In July 2023 patient was hospitalised for venetoclax ramp-up, while during the physical examination a 2.5 cm tumefaction in left breast was found. Biopsy confirmed ductal invasive breast carcinoma. After tumorectomy adjuvant use of letrozole was implemented. Venetoclax ramp-up began in November 2023 (Le 177x10⁹/L, Hb 105 g/L, Tr 65x10⁹/L; lymphadenopathy up to 3 cm; splenomegaly 6 cm below costal margin). Venetoclax ramp-up concluded in December 2023 (Le 3.63x10⁹/L, Hb 97 g/L, Tr 261x10⁹/L), with persistent lymphadenopathy up to 1.5 cm.

Conclusion: During watch-and-wait and treatment CLL patients' comorbidities, drug toxicity and potential malignancy should always be reevaluated.

Keywords: CLL, ibrutinib, venetoclax, cardiotoxicity, malignancy

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ZNAČAJ KONVENCIONALNE CITOGENETIČKE ANALIZE U HRONIČNOJ LIMFOCITNOJ LEUKEMIJI; ISKUSTVO KLINIKE ZA HEMATOLOGIJU UKCS

THE SIGNIFICANCE OF CONVENTIONAL CYTOGENETIC ANALYSIS IN CHRONIC LYMPHOCYTIC LEUKEMIA; EXPERIENCE OF THE CLINIC FOR HEMATOLOGY, UCCS

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SAŽETAK

Uvod: Prva saznanja o genetičkoj heterogenosti hronične limfocitne leukemije (HLL) dobijena su početkom '90-ih godina XX veka zahvaljujući konvencionalnoj citogenetičkoj analizi. Kako je B limfocit, zrela ćelija, neophodna je stimulacija na deobu. Kao B mitogeni korišćeni su poliklonalni B ćelijski aktivator (EBV), lipopolisaharid iz *E. coli*, pokweed, CD-40 ligand, interleukini, međutim, citogenetička analiza je bila moguća kod 40-60% bolesnika. Otkrivene su citogenetičke aberacije koje imaju prognostički značaj (del13q14, +12, del11q22 i del17p13), one su inkorporirane u metodu interfazne fluorescentne in situ hibridizacije (iFISH). Upotrebom novih B mitogena, kao što je kombinacija imunostimulatornih CpG oligonukleotida i inetreleukina 2 (IL-2) omogućeno je da kod 90% bolesnika uradimo konvencionalnu citogenetičku analizu.

Cilj: Prikazati rezultate citogenetičke analize i ukazati na značaj dobijenih informacija u boljoj stratifikaciji i lečenju HLL bolesnika.

Metode: Od januara 2019. do juna 2024. godine u Laboratoriji za citogenetiku i molekularnu genetiku, Klinike za hematologiju UKCS, konvencionalna citogenetička analiza je urađena na 455 uzoraka periferne krvi bolesnika sa HLL-om, prosečne starosti 65 godina, sa predominacijom bolesnika muškog pola (63,1%). Za stimulaciju B limfocita korišćena je kombinacija imunostimulatornog CpG oligonukleotida (DSP-30) i IL-2.

Rezultati: Mitoze za citogenetičku analizu smo dobili kod 409 od 455 obrađenih uzoraka (89,9%). Normalan kariotip je detektovan kod 129 (31,5%), aberantan kariotip je imao 281 analizirani uzorak (68,5%). Kompleksne aberacije (≥ 5) smo detektovali kod 16 bolesnika (5,7%), grupa veoma visokog rizika.

Zaključak: Konvencionalna citogenetička analiza nam daje dodatne informacije o genetičkim promenama u HLL i tako omogućava da bolje stratifikujemo i lečimo naše bolesnike.

Ključne reči: hronična limfocitna leukemija, konvencionalna citogenetika, imunostimulatorni CpG oligonukleotidi, kompleksan kariotip

ABSTRACT

Introduction: In the early 1990s, conventional cytogenetic analysis revealed the genetic heterogeneity of chronic lymphocytic leukemia (CLL). B lymphocytes, being mature cells, lack the ability to divide and require stimulation. Initially, B mitogens like EBV, *E. coli* lipopolysaccharide, pokeweed, CD-40 ligand, and various interleukins were used, enabling cytogenetic analysis in 40-60% of patients. Cytogenetic aberrations with prognostic significance (deletion 13q14, trisomy 12, deletion 11q22, and deletion 17p13) were identified and incorporated into interphase fluorescent in situ hybridization (iFISH). New B mitogens, such as immunostimulatory CpG oligonucleotides combined with interleukin 2 (IL-2), have improved the success rate of conventional cytogenetic analysis to 90%.

Objective: To present cytogenetic analysis results and emphasize their significance for the stratification and treatment of CLL patients.

Methods: From January 2019 to June 2024, 455 peripheral blood samples from CLL patients were analyzed at the Laboratory for Cytogenetics and Molecular Genetics, Clinic for Hematology, UCCS. The average patient age was 65 years, with a male predominance of 63.1%. Immunostimulatory CpG oligonucleotide (DSP-30) and IL-2 were used for stimulation B-cells.

Results: Mitoses for cytogenetic analysis were obtained from 409 out of 455 processed samples (89.9%). Among these, 129 (31.5%) showed a normal karyotype, while 281 (68.5%) exhibited aberrant karyotypes. Complex aberrations (≥ 5) were detected in 16 patients (5.7%), indicating a high-risk group.

Conclusion: Conventional cytogenetic analysis provides additional genetic information in CLL, enhancing patient stratification and treatment.

Keywords: chronic lymphocytic leukemia, conventional cytogenetics, immunostimulatory CpG oligonucleotides, complex karyotype

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EXACERBATION OF AUTOIMMUNE HEMOLYTIC ANEMIA IN A PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA DURING IBRUTINIB THERAPY

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SAŽETAK

Uvod: Manifestacija hronične limfocitne leukemije je i autoimuna hemolizna anemija. Tokom započinjanja lečenja ibrutinibom dolazi do razvoja limfocitoze koja može uzokovati povećanje antitela odgovornih za nastanak hemolize.

Cilj: Prikazati klinički tok našeg bolesnika.

Metode: Podaci su dobijeni iz medicinske dokumentacije.

Rezultati: Bolesniku je u 77. godini života dijagnostikovana CLL na osnovu imunofenotipa ćelija periferne krvi CD38+CD49d+, HLL scor 5, u CS A, bez komorbiditeta, ambulantno praćen. Nakon 18 meseci uvećanje limfadenopatije sa porastom broja leukocita i razvojem autoimune hemolizne anemije. Lečen sa dva ciklusa protokola COP uz smanjenje limfadenopatije i broja leukocita, 25 do 30 x10⁹/L, Coombs negativan. FISH detektuje u 90% nukleusa deleciju regiona 17p (TP53 gena), u 40% deleciju 13q14. Započeta je terapija ibrutinibom. Četrnaestog dana lečenja leukociti su 50 x10⁹/L, hemoglobin 115 g/L, osamnaestog pojava tamne mokraće uz opštu slabost leukociti su 156 x10⁹/L, hemoglobin 44 g/L, LDH 1500. Pacijent je hospitalizovan, Coombs je pozitivan, ordinirana terapija kortikosteroidima 2 mg/kg tt uz svu suportivnu terapiju i dve transfuzije eritrocita. Nakon 12h pad hemoglobina na 30 g/L, dolazi do cardiac arrest-a i smrti.

Zaključak: Uz druge neželjene efekte ibrutiniba, moguć je razvoj iznenadne, teške egzacerbacije hemolizne anemije.

Ključne reči: hronična limfocitna leukemija, autoimuna hemolizna anemija, ibrutinib

ABSTRACT

Introduction: A manifestation of chronic lymphocytic leukemia is autoimmune hemolytic anemia. During the initiation of treatment with ibrutinib, the development of lymphocytosis occurs, which can cause an increase in the antibodies responsible for the occurrence of hemolysis.

Objective: To show the clinical course of our patient.

Methods: Data were obtained from medical records.

Results: At the age of 77, the patient was diagnosed with CLL based on the immunophenotype of peripheral blood cells CD38+CD49d+, HLL score 5, in CS A, without comorbidities, outpatient follow-up. After 18 months, an increase in lymphadenopathy with an increase in the number of leukocytes and the development of autoimmune hemolytic anemia. Treated with two cycles of COP protocol with reduction in lymphadenopathy and leukocyte count, 25 to 30 x10⁹/L, Coombs negative. FISH detects deletion of the 17p (TP53 gene) region in 90% of nuclei, 13q14 deletion in 40%. Ibrutinib therapy was started. On the fourteenth day of treatment, leukocytes are 50 x10⁹/L, hemoglobin 115 g/L, on the eighteenth appearance of dark urine with general weakness, leukocytes are 156 x10⁹/L, hemoglobin 44 g/L, LDH 1500. The patient is hospitalized, Coombs is positive, corticosteroid therapy 2 mg/kg of body weight is prescribed with all supportive therapy and two erythrocyte transfusions. After 12 hours, the hemoglobin drops to 30 g/L, leading to cardiac arrest and death.

Conclusion: In addition to other side effects of ibrutinib, the development of a sudden, severe exacerbation of hemolytic anemia is possible.

Keywords: chronic lymphocytic leukemia, autoimmune hemolytic anemia, ibrutinib

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TREATMENT RESULTS OF PATIENTS WITH HAIRY CELL LEUKEMIA – EXPERIENCES FROM UNIVERSITY HOSPITAL MEDICAL CENTER BEZANIJSKA KOSA

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SAŽETAK

Uvod: HCL je hronična indolentna B ćelijska neoplazma prvi put opisana 1958. od Bouroncle i sar. Primena purinskih analoga dovela je do odličnih rezultata u lečenju ove bolesti.

Cilj: Analiza parametara, odgovora na terapiju i preživljavanja bolesnika sa HCL.

Metode: Radi se o retrospektivnoj analizi bolesnika. Analiza podataka rađena je deskriptivnom statistikom, a za preživljavanje je korišćena metoda Kaplan-Majer.

Rezultati: U periodu od 2009.-2024. lečeno je 18 bolesnika starosti 38–94 god. Na prezentaciji broj leukocita se kretao u opsegu od $1,4\text{--}12,1 \times 10^9/\text{L}$, neutrofila $0,23\text{--}2,25 \times 10^9/\text{L}$, limfocita $0,55\text{--}6 \times 10^9/\text{L}$, Hb od 52 g/L do 141 g/L /medijana 110 g/L, trombocita od 27 do $322 \times 10^9/\text{L}$ /medijana $94 \times 10^9/\text{L}$. Tri pacijenta su zahtevala primenu transfuzija koncentrovanih eritrocita. Splenomegaliju je imalo 64%. Infiltracija koštane srži je bila prosečno 75%. Lečenje cladribinom je primenjeno kod većine bolesnika, jedan nije lečen, a jedna je zbog istovremeno prisutnog kompozitnog difuznog B limfoma lečena po R-CHOP HT protokolu. Trajanje neutropenije je bilo oko 20 dana /od 5 do 34 /, febrilnu neutropeniju je imalo 53% pacijenata. Povoljan terapijski odgovor je postignut kod svih bolesnika, kompletan kod 12, parcijalni kod 4. Kod bolesnika kod kojih je postignuta PR sproveden je retreatman cladribinom nakon čega je postignuta CR. Preživljavanje bolesnika je od 7 do 166 meseci. Jedna pacijentkinja je razvila sekundarni malignitet (karcinom kolona), jedna je preminula od KOVID-19 infekcije, a jedna od progresije difuznog B krupnoćelijskog limfoma.

Zaključak: Klinički podaci naših 18 pacijenata sa HCL, terapijski odgovor i preživljavanje su u potpunosti u korelaciji sa literaturnim podacima.

Ključne reči: hairy cell leukemia, rezultati lečenja, klinički podaci

ABSTRACT

Introduction: HCL is a chronic indolent B-cell neoplasm first described in 1958 by Bouroncle et al. The use of purine analogs has led to excellent results in treating this disease.

Objective: Analysis of parameters, response to therapy and survival of patients with HCL.

Methods: Retrospective analysis. Clinical data were analyzed using descriptive statistics, Kaplan-Meier method was used for survival analysis.

Results: From 2009 to 2024 the Hematology Department treated 18 patients ranging in age from 38 to 94 years. Initial laboratory findings showed leukocyte counts ranging from 1.4 to $12.1 \times 10^9/\text{L}$, neutrophils from 0.23 to $2.25 \times 10^9/\text{L}$, lymphocytes from 0.55 to $6 \times 10^9/\text{L}$, hemoglobin from 52 g/L to 141 g/L and platelets from 27 to $322 \times 10^9/\text{L}$. Three patients required red blood cell transfusions. Splenomegaly was present in 64%, bone marrow infiltration in 75%. The standard treatment regimen with cladribine was used, one patient did not receive treatment and one with concomitant diffuse large B-cell lymphoma was treated with R-CHOP protocol. The average duration of neutropenia was approximately 20 days and 53% experienced febrile neutropenia. Favorable therapeutic responses were achieved in all patients, with CR in 71% and PR in 4 patients. Patients achieving PR underwent cladribine retreatment, resulting in CR. Survival ranged from 7 to 166 months.

Conclusion: The clinical data of our 18 patients with hairy cell leukemia, their therapeutic responses, and survival outcomes are fully consistent with literature data.

Keywords: hairy cell leukemia, treatment results, clinical data

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LONG TERM FOLLOW-UP OF HAIRY CELL LEUKEMIA TREATMENT: 30-YEAR EXPERIENCE AT SINGLE UNIVERSITY CENTER

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SAŽETAK

Uvod: Hairy cell leukemia (HCL) je retka limfoproliferativna bolest sa povoljnom prognozom. Sekundarni maligniteti (SM) su zabeleženi kod pacijenata sa HCL-om, ali iziskuju dodatne studije.

Cilj: Identifikacija faktora koji utiču na preživljavanje, terapijski odgovor i SM kod pacijenata sa HCL.

Metode: Uključeno je 211 pacijenata sa HCL-om lečenih od 1993. do 2023. godine (medijana praćenja 108 meseci). Analizirani su faktori poput godina, pola, laboratorijskih nalaza, hepatosplenomegalija, tipa terapije, pojave SM, ukupnog preživljavanja (OS) i uzroka smrti. Pacijenti su podeljeni u dve grupe: Grupa A (119 pacijenata) primila je jednu terapijsku liniju (1TL 2-hlorodeoksadenozina), dok je Grupa B (80 pacijenata) primila ≥ 2 TL.

Rezultati: Medijana godina na dijagnozi iznosila je 54 godine. U grupi A, 87,5% je postiglo kompletnu remisiju (CR) (medijana 91 mesec). U grupi B, stope CR bile su 77,1%, sa medijanom trajanja prve, druge i treće remisije od 49, 73 i 83 meseca. Multivarijatna analiza je identifikovala uzrast i SM kao prediktore za višestruku TL. OS je značajno bio duži u grupi B (324 meseci naspram 250 meseci, $p < 0,001$). SM su verifikovani kod 16,7% pacijenata. Mlađa životna dob i terapija interferonom alfa-2a su bili prediktivni za SM. Stopa preživljavanja nakon 5, 10 i 15 godina bila je 86,3%, 72,7% i 61,6%. Glavni uzroci smrti bili su srčana insuficijencija i SM (70%).

Zaključak: Mlađi uzrast i SM su bili značajni faktori rizika za relaps. Takođe, uzrast i terapija interferonom su bili prediktori za SM. Uprkos češćim relapsima kod mlađih pacijenata, OS se nije značajno razlikovao u poređenju sa pacijentima koji su primili 1TL.

Ključne reči: hairy cell leukemia, sekundarni maligniteti, kladribin, interferon

ABSTRACT

Introduction: Hairy cell leukemia (HCL) is a rare lymphoproliferative disease with a favorable prognosis. Secondary malignancies (SM) are reported in HCL patients, but more data is needed.

Objective: This study aimed to identify factors influencing response, survival, and SM development in HCL.

Methods: We studied 211 HCL patients treated from 1993. to 2023., with a median follow-up of 108 months. Factors including age, gender, laboratory findings, hepatosplenomegaly, treatment, SM occurrence, overall survival (OS), and causes of death were analyzed. Patients were divided into two groups: Group A (119 patients) received one treatment line (1TL of 2-chlorodeoxyadenosine), while Group B (80 patients) received ≥ 2 TL.

Results: Median age at diagnosis was 54 years. In group A, 87.5% achieved complete remission (CR) with median remission duration of 91 months. In group B, CR rates were 77.1% with first, second and third remission median durations of 49, 73, and 83 months. Multivariate analysis identified younger age and SM as predictors for multiple TL. OS was significantly longer in group B (324 months vs. 250 months, $p < 0.001$). SM occurred in 16.7% of patients, predominantly solid tumors. Age and interferon alfa-2a treatment were significant risk factors for SM. Survival rates at 5, 10, and 15 years were 86.3%, 72.7%, and 61.6%, respectively. Causes of death were mainly heart failure and SM (70%).

Conclusion: Younger age and SM were significant risk factors for relapse. Age and interferon treatment were predictors for SM occurrence. Despite more frequent relapses in younger patients, OS did not differ significantly from those with one TL.

Keywords: hairy cell leukemia, secondary malignancies, cladribine, interferon

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NE-HOČKINOV LIMFOM

NON-HODGKIN LYMPHOMA

CASE REPORT: ISOLATED CNS RELAPS OF MANTLE CELL LYMPHOMA

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SAŽETAK

Uvod: Mantle cell lymphoma predstavlja rijetku i agresivnu formu ne-Hoćkino-vog limfoma. Obično se javlja kod ljudi starije životne dobi. Najčešće ektranodal-ne lokalizacije bolesti su digestivni trakt i jetra.

Prikaz slućaja: Muškarac, 69 godina, na prezentaciji bolesti sa izraženim noćnim preznojavanjem, malaksalost i gubitak u tjelesnoj težini. Postavljena dijagnoza Mantle cell limfoma CSIV B, MIPI 7.9, sa splenomegalijom i retroperitonealnom i medijastinalnom limfadenopatijom. Sprovedeno lijećenje po R-CHOP protokolu (VI ciklusa) uz postizanje kompletne remisije bolesti. Nakon pet mjeseci javlja se na pregled neurologa i interniste zbog bolova u desnoj polovini glave, duplih slika i ptoze lijevog oćnog kapka i jakih bolova u abdomenu. U laboratorijskim analizama povišen LDH uz urednu krvnu sliku. Urađen MSCT endokranijuma sa angiografijom ukazao samo na laku stenozu arterie carotis interne. Nalaz MSCT-a grudnog koša, abdomena i male karlice, kao i ultrazvuka perifernih regija nije ukazao na relaps oboljenja. U više navrata pokušana kolonoskopija koja nije urađena zbog "neadekvatne pripreme", te postavljena sumnja na neurološku enteropatiju. Urađena lumbalna punkcija. Likvor upućen na obradu protoćnom citofluorimetrijom. Prestigli nalaz ukazao na prisustvo populacije atipićnih monoklonalnih zrelih B-ćelija (97,7% limfocita likvora), koje karakteriše niska vrijednost HLL skora, što moće uputiti na dg. B-NHL/CD5+CD10+. Zakljućeno da se radi o izolovanom CNS relapsu. Odlućeno da se sprovede lijećenje inhibitorom tirozin kinaze (ibrutinib).

Zakljućak: Izolovano zahvatanje centralnog nervnog sistema kod relapsa Mantle cell limfoma je dosta rijetka manifestacija bolesti o kojoj treba misliti.

Kljućne reći: mantle cell limfom, CNS relaps, R-CHOP, inhibitor tirozin kinaze, ibrutinib

ABSTRACT

Introduction: Mantle cell lymphoma is a rare and aggressive type of non-Hodgkin lymphoma, primarily affecting elderly individuals. It often manifests in extranodal locations, such as the digestive tract and liver.

Case report: A 69-year-old man presented with severe night sweats and weight loss. He was diagnosed with Mantle cell lymphoma, CSIV B, MIPI 7.9, featuring splenomegaly and retroperitoneal and mediastinal lymphadenopathy. After six cycles of the R-CHOP protocol, complete remission was achieved. Five months later, he experienced right-sided head pain, double vision, ptosis of the left eyelid, and abdominal pain. Laboratory analyses revealed elevated LDH but a normal blood count. MSCT of the head with angiography showed mild internal carotid artery stenosis. Further MSCT scans of the chest, abdomen, and pelvis, along with a peripheral ultrasound, did not indicate disease relapse. Despite several attempts, colonoscopy was unsuccessful due to inadequate preparation, raising suspicion of neurological enteropathy. A lumbar puncture was performed, and cerebrospinal fluid analysis via flow cytometry suggested B-NHL/CD5+CD10+. It was concluded that the patient had an isolated CNS relapse. Treatment with a tyrosine kinase inhibitor, ibrutinib, was initiated.

Conclusion: Isolated central nervous system involvement in relapsed Mantle cell lymphoma is a rare occurrence that warrants consideration during diagnosis and treatment.

Keywords: Mantle cell lymphoma, CNS relapse, R-CHOP, tyrosine kinase inhibitor, ibrutinib

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PRIMARY OCULAR-ADNEXAL MUCOSA-ASSOCIATED LYMPHOID TISSUE LYMPHOMA – SINGLE CENTER TWENTY-YEAR EXPERIENCE

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SAŽETAK

Uvod: Limfomi orbite i okularnih adneksa čine 2% svih ne-Hoćkinovih limfoma. Najčešći podtip je MALT (Mucosa-Associated Lymphoid Tissue) limfom. Autoimuni inflamatorni poremećaji i hronične infekcije mogu biti važni etiološki faktori. Inicijalni simptomi bolesti se mogu pojaviti značajno pre dijagnoze. Dostupne su različite terapije opcije.

Cilj: Predstaviti rezultate dvadesetogodišnje retrospektivne analize, epidemiološko-demografske, kliničke i laboratorijske karakteristike, efikasnost različitih terapijskih opcija i ishod lečenja.

Metode: U našu analizu je uključeno 32 pacijenta sa MALT orbite i okularnih adneksa. Korišćene su metode parametarske i neparametarske statistike sa akcentom na deskriptivne statističke analize.

Rezultati: Najveća incidenca je registrovana u osmoj deceniji, češće kod muškaraca. Simptomi bolesti su heterogeni, medijana perioda od pojave simptoma do dijagnoze je 9 meseci. Inflamatorni parametri su u proseku uredni. Nije potvrđen prediktivni značaj sialoforina. Svi pacijenti su imali lokalizovanu bolest, najčešće u mekom tkivu orbite, i stratifikovani su u grupu niskog ili srednje niskog rizika. Najbolji inicijalni terapijski ishod je bio postignut hemo ili radio terapijom. Sistemsku ili lokalnu progresiju bolesti je imalo 50% pacijenata. Registrovali smo dobar terapijski ishod u lečenju progresije/ relapsa primenom hemo ili radioterapije. „High grade“ transformacija je otkrivena u 6,25% slučajeva. Petogodišnje ukupno preživljavanje je iznosilo 100%, desetogodišnje 88% (medijana perioda praćenja 112,5 meseci). Petogodišnji period bez progresije bolesti je iznosio 65%, a desetogodišnji 48%.

Zaključak: Naši rezultati potvrđuju da je MALT orbite i okularnih adneksa indolentan limfom sa dobrim ukupnim terapijskim odgovorom. Neophodne su redovne kontrole pacijenata nakon inicijalne remisije, zbog značajnog stepena progresije bolesti i mogućnosti „high grade“ transformacije.

Ključne reči: ne-Hoćkinov limfom, orbita, hemoterapija

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ABSTRACT

Introduction: Ocular adnexal lymphomas consist 2% of non-Hodgkin lymphomas. The most frequent is MALT (Mucosa-Associated Lymphoid Tissue) Lymphoma (OAML). Autoimmune inflammatory disorders and chronic infections can be important etiological factors. Initial disease signs and symptoms can appear much before OAML diagnosis. Various therapy options are available.

Objective: To present results of twenty-year period retrospective analysis, including epidemiologic-demographic, clinical and laboratory characteristics, various treatment options effectiveness and disease outcome.

Methods: We enrolled 32 OAML patients. Methods of parametric and non-parametric statistics were used with accent on descriptive statistical analyses.

Conclusion: The highest incidence was in 8th decade, more frequent in males. Initial signs and symptoms were heterogeneous, and median period from their appearance to diagnosis was 9 months. In average, inflammatory parameters were normal. No predictive significance of sialophorin was confirmed. All patients had localized disease, most frequently in orbit soft tissue, and were stratified in low or intermediate low risk group. Best initial disease control was confirmed with chemo or radio therapy. Systemic or local disease progression had 50% of patients. We concluded good disease control in progression/relapse treatment with chemo or radiotherapy. „High grade“ transformation was detected in 6.25%. 5-Year overall survival was 100% and 10-Year was 88% (median follow-up 112.5 months). 5-Year progression free survival was 65% and 10-Year was 48%.

Conclusion: Our results confirm that OAML is and indolent lymphoma with good overall therapy response. Nevertheless, it acquires regular patient check-ups after initial remission, due to significant disease progression rate and „high grade“ transformation possibility.

Keywords: non-Hodgkin lymphoma, orbit, chemotherapy

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TREATMENT OF FOLLICULAR LYMPHOMA WITH OBINUTUZUMAB – EXPERIENCE OF THE CLINICAL CENTER OF VOJVODINA

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SAŽETAK

Uvod: Obinutuzumab u kombinaciji sa citostatskim protokolima se koristi za lečenje bolesnika sa folikularnim limfomom.

Cilj: Analiza laboratorijskih, kliničkih parametara i odgovora na terapiju kod bolesnika lečenih sa obinutuzumab -citostatskim protokolima.

Metode: Sprovedena je retrospektivna analiza podataka prikupljenih iz istorija bolesti i pokliničkih kartona bolesnika. Podaci su obrađeni metodama deskriptivne statistike.

Rezultati: Na Klinici za hematologiju, u periodu od 2020. do 2024. godine, je 12 bolesnika primilo obinutuzumab u sklopu antilimfomskog protokola, od kojih je bilo 4 muškaraca i 8 žena, prosečne starosti 55 godina. Deset bolesnika je imalo klinički stadijum III i IV, dok su dva bolesnika bila u II kliničkom stadijumu ali sa „bulky” bolešću. Korišćeni su GELF kriterijumu za odluku o započinjanju lečenja, 6 bolesnika je imalo jedan pozitivan GELF kriterijum. Bolesnici su prema FLIPI skoru podeljeni u grupe niskog rizika – 4 bolesnika, intermedijarnog – 3 i visokog rizika 5 bolesnika. Kod 4 bolesnika se FLIPI i FLIPI2 skor podudaraju, dok kod ostalih bolesnika FLIPI2 skor pokazuje viši nivo rizika. Četvoro bolesnika je završilo terapiju i terapiju održavanja, čime je postignuta remisija, bez znakova relapsa bolesti u praćenju. Petoro bolesnika prima terapiju održavanja, dok je tri bolesnika u procesu aktivnog lečenja. Trenutno nisu uočena neželjena dejstva obinutuzumaba koji bi dovela do obustave terapije.

Zaključak: Obinutuzumab se pokazao efikasnim u cilju postizanja remisije kod bolesnika sa folikularnim limfomom. Potrebno je dugoročno praćenje ovih bolesnika radi utvrđivanja dužine remisije i ukupnog preživljavanja.

Ključne reči: obinutuzumab, folikularni limfom, terapijski odgovor

ABSTRACT

Introduction: Obinutuzumab in combination with cytostatic protocols is used for the treatment of patients with follicular lymphoma.

Objective: Analysis of laboratory, clinical parameters and response to therapy in patients treated with obinutuzumab -cytostatic protocols.

Methods: A retrospective analysis of data collected from medical records of patients was conducted. The data were processed using the methods of descriptive statistics.

Results: At the Hematology Clinic, in the period 2020–2024, 12 patients received obinutuzumab as part of the anti-lymphoma protocol, 4 men and 8 women, average age of 55 years. Ten patients had clinical stage III and IV, while two patients had clinical stage II but with “bulky” disease. GELF criteria were used for the decision to start treatment, 6 patients had 1 positive GELF criteria. According to the FLIPI score, the patients were divided into groups of low risk – 4 patients, intermediate – 3 and high risk – 5 patients. In 4 patients, the FLIPI and FLIPI2 scores match, while in other patients the FLIPI2 score shows a higher level of risk. Four patients completed therapy and maintenance therapy, achieved remission, without relapse during follow-up. Five patients are receiving maintenance therapy, three patients are in the process of active treatment. Currently, no adverse effects of obinutuzumab that would lead to discontinuation of therapy have been observed.

Conclusion: Obinutuzumab was effective in achieving remission in patients with follicular lymphoma. Long-term follow-up of these patients is necessary to determine the length of remission and overall survival.

Keywords: obinutuzumab, follicular lymphoma, therapeutic response

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PROGNOSTIČKI ZNAČAJ LABORATORIJSKOG PROGNOSTIČKOG INDEKSA (LAPI) KOD OBOLELIH OD DIFUZNOG B-KRUPNOĆELIJSKOG LIMFOMA

PROGNOSTIC SIGNIFICANCE OF LABORATORY PROGNOSTIC INDEX (LAPI) IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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SAŽETAK

Uvod: Laboratorijski prognostički indeks (LaPI) predstavlja prognostički indeks koji se koristi za predviđanje ishoda bolesti kod obolelih od difuznog B-krupnoćelijskog limfoma (DBKL). Značaj ovog indeksa ogleda se u jednostavnosti njegovog određivanja koje podrazumeva analizu tri laboratorijska parametra pri postavljanju dijagnoze DBKL: laktat dehidrogenaze (LDH), hemoglobin (Hb) i beta-2 mikroglobulina (B2M).

Cilj: Cilj ovog istraživanja bio je utvrditi prognostički značaj LaPI kod bolesnika sa novodijagnostikovanim DBKL.

Metode: Retrospektivna analiza je obuhvatila 219 bolesnika sa novodijagnostikovanim DBKL lečenih u Kliničkom centru Vojvodine od 2010. godine do juna 2024. godine. Podaci su prikupljeni iz medicinske dokumentacije. Za određivanje LaPI korišćene su vrednosti LDH, Hb i B2M.

Rezultati: Medijana starosti je bila 64 godine. Muškarci su činili 54,7% ispitanika. Medijana ukupnog preživljavanja (OS) je bila 20,5 meseci, a medijana preživljavanja bez progresije bolesti (PFS) 11 meseci. Preminulo je 17% ispitanika, a relaps ili progresija bolesti su verifikovani u 21,8%. LaPI 0 je imalo 16% ispitanika, LaPI 1 25% ispitanika, kod 25,9% je LaPI bio 2, LaPI 3 je imalo 22,2% a LaPI 4 18,9% ispitanika. Niža vrednost LaPI je bila statistički značajno povezana sa nižim rizikom prema IPI (χ^2 (1, N) = 18,55, $p < 0.0001$), R-IPI (χ^2 (1, N) = 32,21, $p < 0.0001$) i NCCN-IPI skorovima (χ^2 (1, N) = 8,36, $p = 0,0038$). Univarijantnom analizom (log-rank test), vrednost LaPI je imala statistički značajan uticaj na OS (HR(95% CI) 0,2373(0,1134–0,4968), $p = 0,0001$).

Zaključak: Niže vrednosti LaPI koreliraju sa nižim rizikom prema IPI, R-IPI i NCCN-IPI skorovima. Vrednost LaPI značajno utiče na ukupno preživljavanje obolelih od novodijagnostikovanog DBKL.

Ključne reči: difuzni B-krupnoćelijski limfom, prognoza, LaPI

ABSTRACT

Introduction: LaPI is a prognostic index used to predict disease outcomes in patients with diffuse large B-cell lymphoma (DLBCL). Its significance lies in its simplicity of determination, which involves analyzing three laboratory parameters at DLBCL diagnosis: lactate dehydrogenase (LDH), hemoglobin (Hb), and beta-2 microglobulin (B2M).

Objective: This study aimed to ascertain the prognostic significance of LaPI in patients newly diagnosed with DLBCL.

Methods: A retrospective analysis included 219 patients newly diagnosed with DLBCL treated at the Clinical Center of Vojvodina from 2010 to June 2024. The values of LDH, Hb and B2M were used to determine LaPI.

Results: The median age was 64 years. Male participants comprised 54.7% of the cohort. The median overall survival (OS) was 20.5 months, and the median progression-free survival (PFS) was 11 months. A total of 17% of participants were deceased, while relapse or disease progression was verified in 21.8%. LaPI score of 0 was observed in 16% of participants, a score of 1 in 25%, a score of 2 in 25.9%, a score of 3 in 22.2%, and a score of 4 in 18.9%. Lower LaPI score was statistically significantly associated with lower risk according to IPI (χ^2 (1, N) = 18.55, $p < 0.0001$), R-IPI (χ^2 (1, N) = 32.21, $p < 0.0001$) and NCCN-IPI (χ^2 (1, N) = 8.36, $p = 0.0038$) scores. In univariate analysis (log-rank test), LaPI score significantly impacted OS (HR(95% CI) 0.2373(0.1134–0.4968), $p = 0.0001$).

Conclusion: Lower LaPI values correlate with lower risk according to IPI, R-IPI, and NCCN-IPI scores. LaPI score significantly impacts the overall survival of DLBCL.

Keywords: diffuse large B-cell lymphoma, prognosis, LaPI

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NON-HODGKIN LYMPHOMA IN CARDIAC TISSUE, DIAGNOSTIC DILLEMAS AND THERAPY CHALLENGES: CASE REPORT

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SAŽETAK

Uvod: Primarni limfomi srčanog tkiva (najčešće NHL DBKL), čine 0,5% ekstranodalnih limfoma. Najčešće infiltrišu desnu prekomoru i komoru (DK). Prezentuju se dispnejom, aritmijama, kongestivnom srčanom insuficijencijom i perikardnim izlivima. Dijagnostika uključuje direktnu biopsiju tumora. Nepovoljni dijagnostički faktori su imunodeficijencija, infiltracija leve komore (LK), aritmije i ekstrakardijalna limfomska infiltracija. Hemoterapija predstavlja najefikasniji modalitet.

Cilj: Prezentovanje dijagnostičkih dilema i izazova u lečenju pacijentkinje sa limfomom srčanog tkiva.

Metode: Pacijentkinja je dijagnostikovana i lečena u okviru našeg Kliničkog centra, na hematologiji, kardiologiji i kardiovaskularnoj hirurgiji. Dijagnostika je uključivala laboratorijske i radiografske analize, biopsije tumora i koštane srži.

Rezultati: Pacijentkinja uzrasta 70 godina je inicijalno hospitalizovana maja 2023. na kardiologiji, zbog stenokardije, umora i dispneje. UZ srca je pokazao perikardni izliv, hipertrofiju DK, mogući tromb LK, MSCT angiografija prisustvo embolusa plućnog arterijskog stabla. Ponovljen UZ srca detektuje mogući perikardni i tumor izlaznog trakta DK. Učinjene biopsije perikardijalnih i intramuralnih lezija potvrdile su DBKL. Postoperativni MSCT registruje tumor ispred pulmonalnog trakta (41x53 mm) sa propagacijom u DK (39x50 mm), miokardne lezije LK (44x51 mm) i DK (38x50 mm). Hematološkim ispitivanjem je utvrđen ekstranodalni limfom srčanog tkiva, NHL DBKL. Tokom primene deksazona dolazi do pojave ventrikularnih ekstrasistola i atrijske fibrilacije (AF). Nakon farmakološke konverzije AF, primenjena je prva COEP hemioterapija, međutim nakon kratkog kliničkog poboljšanja, srčana disfunkcija je progredirala sa mogućom trombotičnom epizodom (uz antikoagulanse) i fatalnim ishodom.

Zaključak: Ukupno preživljavanje nelečenog limfoma srčanog tkiva je manje od mesec dana. Pravovremena dijagnostika je ključna. Uprkos savremenom boljem ishodu lečenja, kasna dijagnostika i prisustvo negativnih prognostičkih faktora značajno redukuju efikasnost lečenja.

Ključne reči: ne-Hoćkinov limfom, ekstranodalna lokalizacija, hemoterapija, leva komora

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ABSTRACT

Introduction: Primary cardiac lymphoma (PCL) consists only 0.5% of extranodal lymphomas, most frequent is NHL DLBCL. Most commonly involved are right atrium and ventricle (RV), presenting with dyspnea, arrhythmia, congestive heart failure and pericard effusion. Diagnostics includes tumor biopsy. Adverse prognostic factors are immunodeficiency, arrhythmia, left ventricle (LV) and extra-cardiac involvement. Chemotherapy is most efficient.

Objective: to present diagnostic dilemmas and treatment challenges in our patient with lymphoma case.

Methods: Patient was diagnosed and treated in our Clinical Centre, in Hematology, Cardiology and Cardiovascular Surgery. Diagnostics included laboratory, radiography, tumor and bone marrow biopsies.

Results: Female patient (70) was initially diagnosed (May 2023) in Cardiology, due to chest pain, fatigue and dyspnea. TTE showed pericardial effusion, RV hypertrophy and possible LV thrombus. Pulmonary artery MSCT proved pulmonary trunk defect. Repeated TTE revealed possible pericardial and RVOT tumor. Subsequent pericardial and intramural lesions biopsies confirmed DLBCL. Post-surgery MSCT showed tumor in front of pulmonary tract (41x53 mm), propagating into RV (39x50 mm), LV (44x51 mm) and RV (38x50 mm) myocardial lesions. Hematological examination confirmed extranodal cardiac NHL DLBCL. During dexamethasone treatment, ventricular extra systoles and atrial fibrillation (AF) occurred. Following pharmacologic AF conversion, patient received first COEP regimen, but following brief clinical improvement, heart dysfunction progressed with possible thrombotic episode (with anticoagulant), resulting in fatal outcome.

Conclusion: If untreated cardiac lymphoma overall survival is less than a month. Prompt diagnostics is crucial. Despite up-to-date better treatment outcome, diagnostics delay and negative prognostic factors can undermine otherwise efficient treatment.

Keywords: non-Hodgkin, extranodal, chemotherapy, left ventricle

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MOSUNETUZUMAB – EXPERIENCE OF OUR CENTER

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SAŽETAK

Uvod: Bispecifična antitela predstavljaju revoluciju u lečenju hematoloških pacijenata. Prikazujemo pacijentkinju koja se u našem centru aktuelno leči mosunetuzumabom.

Prikaz slučaja: Reč je o pacijentkinji starosti 45 godina kod koje je dijagnoza NHL folliculare postavljena biopsijom limfnog nodusa na vratu 2015. godine. Lečena je sa VIII cy RCHOP (poslednji u februaru 2016), nakon čega se postiže kompletna remisija bolesti. Naredne dve godine lečena primenom terapije održavanja (rituksimab). Krajem 2020. godine je registrovana limfadenopatija i učinjena biopsija Igl zbog sumnje na transformaciju. PH nalazom potvrđen prvi relaps i lečenje sprovedeno RFC protokolom u VI cy nakon čega se postiže CR. Ponovljena terapija održavanja rituksimabom. U decembru 2022. godine registrovan drugi relaps bolesti, sada lokalizovana forma – sprovedena RT (3d-CRT sa TD 30G u 10 frakcija). U maju 2023. godine se ponovo registruje, sada treći relaps. Lečena HT po protoklu DHAP u 2 cy, a zatim protokolom ICE (1 ciklus), nakon čega se na PET CT-u održava aktivna bolest. Pacijentkinja je prikazana Etičkom odboru radi nastavka lečenja primenom bispecifičnim At- mosunetuzumabom. Tokom I cy pacijentkinja sve vreme hospitalizovana uz monitoring kliničkog stanja i vitalnih parametara, od komplikacija registrovana epizoda subfebrilnosti koja je kupirana paracetamolom. Nakon IV cy učinjena procena terapijskog odgovora gde je registrovana VGPR. Do sada primila VII cy mosunetuzumaba, redovno se kontroliše ambulantno.

Zaključak: Imajući u vidu prirodu bolesti i dosadašnje modalitete lečenja, kao i dosadašnji odgovor na mosunetuzumab očekujemo da ova terapija uvede našu pacijentkinju u CR, sa nadom da se mogućnost relapse svede na minimum.

Ključne reči: NHL folliculare, relaps, mosunetuzumab

ABSTRACT

Introduction: Bispecific antibodies represent a revolution in the treatment of hematologic patients. We present a patient currently being treated with mosunetuzumab at our center.

Case report: This is a 45-year-old female patient diagnosed with follicular non-Hodgkin lymphoma via a cervical lymph node biopsy in 2015. She was treated with eight cycles of RCHOP achieving complete remission. For the next two years, she received maintenance therapy with rituximab. At the end of 2020, lymphadenopathy was registered. Pathology confirmed the first relapse, and treatment was carried out with the RFC protocol, resulting in complete remission. Maintenance therapy with rituximab was repeated. In December 2022, the second relapse of the disease was registered, now in a localized form, and radiotherapy was conducted. In May 2023, a third relapse was registered. The patient was treated with chemotherapy according to the DHAP protocol, followed by the ICE protocol, after which active disease was still present. The patient was presented to the Ethics Committee for continued treatment with the bispecific antibody mosunetuzumab. During the first cycle, the patient was hospitalized with monitoring of clinical status and vital parameters. Complications included a subfebrile episode. After fourth cycle, a therapeutic response assessment registered a very good partial response. To date, she has received seven cycles of mosunetuzumab and is regularly monitored on an outpatient basis.

Conclusion: Considering the nature of the disease, previous treatment modalities, and the current response to mosunetuzumab, we expect this therapy to induce complete remission in our patient, with the hope of minimizing the possibility of relapse.

Keywords: NHL folliculare, relapse, mosunetuzumab

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MANTLE CELL LYMPHOMA ASSOCIATED WITH COLONIC ADENOCARCINOMA – CASE REPORT

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SAŽETAK

Uvod: Incidenca višestrukih različitih primarnih maligniteta je retka, prema podacima iz literature oko 2-17%. U našoj ustanovi hospitalizovan je pacijent kod koga su dijagnostikovana i lečena dva primarna histološki različita maligniteta, NHL mantle cell i kolorektalni karcinom.

Prikaz slučaja: Reč je o pacijentu starosti 57 godina kod koga je dijagnoza NHL mantle cell u CS II A postavljena 2021. godine, a nakon biopsije limfnog nodusa na vratu. Od hroničnih bolesti, leči se od arterijske hipertenzije. Inicijalno lečenje sprovedeno primenom hemioterapije po protokolu CHOP u VI cy. U septembru 2022. urađena procena terapijskog odgovora i registrovana parcijalna remisija. Pacijent se nakon toga nije javljao hematologu, a krajem ove godine dolazi do pojave gastrointestinalnih tegoba kada je započeto gastroenterološko ispitivanje. Tada je dijagnostikovana de novo maligna bolest – adenokarcinomom colonis invasivum. Pacijent upućen hirurgu i onkologu. Lečen hemioterapijom (po protoklu 5Fu-LV u 3 cy) i zračnom terapijom (TD 50 Gy/25 fr), a zatim i operativno u dva navrata (ELAPE i splenektomija). Početkom 2024. godine pacijent se zbog progresije periferne limfadenopatije javlja hematologu, kada je registrovana progresija bolesti (za 20% porast limfadenopatije na MSCT-u na svim nivoima). Konzilijarno je odlučeno da se lečenje nastavi primenom ibrutiniba u dozi od 560 mg dnevno u četiri ciklusa. Pacijent redovno uzima propisanu terapiju dva meseca unazad i kontroliše se ambulantno kod hematologa i onkologa.

Zaključak: Ishod zavisi od prirode bolesti, kliničkog stadijuma, kao i adekvatnog lečenja. Ovakvi pacijent nas navodi da pojedine tegobe ne pripisujemo osnovnoj bolesti već da ih sve pojedinačno ispitamo.

Ključne reči: NHL mantle cell, adenokarcinom kolona, prikaz slučaja

ABSTRACT

Introduction: The incidence of multiple distinct primary malignancies is rare. We had a patient diagnosed and treated for two primary histologically distinct malignancies, mantle cell lymphoma and colorectal carcinoma.

Case report: This is a 57-year-old patient who was diagnosed with mantle cell lymphoma in CS II A in 2021 after a biopsy of a cervical lymph node. Initial treatment was conducted using chemotherapy according to the CHOP protocol in six cycles. In September 2022, a therapeutic response assessment registered a partial remission. The patient did not visit a hematologist after that, and at the end of the year he developed gastrointestinal symptoms that led to a gastroenterological examination. At that time, other malignant disease – invasive colonic adenocarcinoma – was diagnosed. The patient was referred to a surgeon and oncologist. He was treated with chemotherapy (according to the 5Fu-LV protocol in three cycles) and radiotherapy (TD 50 Gy/25 doses), and then with two surgical interventions (ELAPE and splenectomy). At the beginning of 2024, the patient presented to the hematologist due to the progression of peripheral lymphadenopathy, with a registered 20% increase in lymphadenopathy on MSCT at all levels. It was decided to continue treatment with ibrutinib at a dose of 560 mg daily in four cycles. The patient has been regularly taking the prescribed therapy for the past two months.

Conclusion: The outcome depends on the clinical stage of the disease and adequate treatment. Such patients remind us not to attribute all symptoms to the primary disease but to verify each one individually.

Keywords: mantle cell lymphoma, colonic adenocarcinoma, case report

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PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA: REAL-WORLD DATA OF 7-YEAR SINGLE-CENTER EXPERIENCE SHOW MAJORITY OF PATIENTS IN POOR PERFORMANS STATUS AND POSITIVE IMPACT OF TOTAL/MAXIMAL TUMOR RESECTION ON SURVIVAL

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SAŽETAK

Uvod: Pacijenti sa primarnim limfomom centralnog nervnog sistema (PCNSL) se često prezentuju ograničenom pokretljivošću i lošim opštim stanjem što ih čini nepogodnim za kliničke studije, te je rezultate takvih studija teško tumačiti u kontekstu svakodnevne kliničke prakse.

Cilj: Prezentovati kohortu neselektovanih pacijenata sa PCNSL iz svakodnevne kliničke prakse i analizirati njihove kliničke karakteristike, lečenje i ishod.

Metode: Sproveli smo retrospektivnu studiju na jednom centru analizirajući podatke prikupljene iz dokumentacije 26 pacijenata koji su lečeni u periodu 2017-2023. godine. Pacijenti sa histologijom koja nije difuzni B-krupnoćelijski limfom nisu uzimani u obzir.

Rezultati: Dve trećine (17, 65%) su bili slabog performans statusa (PS) (ECOG 3-4/Karnofsky $\leq 50\%$). Dijagnoza je postavljena nakon totalne ili maksimalne resekcije tumora kod 12 pacijenata (46%). Preživljavanje bez progresije (PFS) je bilo značajno duže kod pacijenata bez venske tromboembolije (VTE) ($p = 0,047$), pacijenata kod kojih je na dijagnozi učinjena totalna ili maksimalna resekcija tumora ($p = 0,008$), kod kojih je kompletirana indukciona terapija ($p < 0,001$), koji su postigli odgovor na indukcionu terapiju ($p < 0,001$) i koji su lečeni konsolidacijom zračnom terapijom (RT) ili autolognom transplantacijom (ASCT) ($p < 0,001$). Totalna ili maksimalna resekcija tumora ($p = 0,035$), kompletiranje ($p < 0,001$) i postizanje odgovora na indukcionu terapiju ($p < 0,001$), konsolidacija RT ili ASCT ($p < 0,001$) pokazali su značajan pozitivan efekat na ukupno preživljavanje.

Zaključak: Značajan broj pacijenata u svakodnevnoj kliničkoj praksi se prezentuje slabim PS. Značajno bolji rezultati lečenja su postignuti ako je inicijalno sprovedena opsežna operacija, odnosno ako je sistemsko lečenje bilo maksimalno (indukcija + konsolidacija).

Ključne reči: primarni limfom centralnog nervnog sistema, performans status, preživljavanje

ABSTRACT

Introduction: Patients with primary central nervous system lymphoma (PCNSL) often present with reduced mobility and poor general condition which make them ineligible for clinical trials, thus leading to results that cannot be extrapolate to real-life.

Objective: To present real-world cohort of unselected PCNSL patients and their clinical and laboratory features, treatment and outcome.

Methods: We conducted single-center retrospective study analysing real-world data from 26 patients managed from 2017 to 2023. Patients with histology other than diffuse large B-cell lymphoma were excluded from the study.

Results: Two thirds (17 patients, 65%) presented with poor performance status (PS) (ECOG 3-4/ Karnofsky index $\leq 50\%$). Diagnosis was made after total tumor extirpation or maximal resection in 12 patients (46%). Progression-free survival was significantly prolonged in patients without VTE ($p = 0.047$), patients who experienced diagnostic total or maximal tumor resection ($p = 0.008$), in those who completed induction treatment ($p < 0.001$), who achieved response after induction treatment ($p < 0.001$) and received consolidative radiotherapy (RT) or autologous stem cell transplant (ASCT) ($p < 0.001$). Total or maximal tumor resection ($p = 0.035$), completion ($p < 0.001$) and response to induction treatment ($p < 0.001$), consolidative RT or ASCT ($p < 0.001$) showed significant positive impact on overall survival.

Conclusion: Significant number of patients in real-world setting are in poor PS. In our cohort survival was significantly affected by VTE, total/maximal tumor resection, completion and achievement of CR/PR to induction treatment, and consolidation. Larger real-world databases are warranted for more reliable conclusions.

Keywords: primary central nervous system lymphoma, performance status, survival

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THE EFFECT OF CYTOPENIA ON THE ADMINISTRATION OF ANTI-LYMPHOMA PROTOCOLS WITH OBINUTUZUMAB IN THE TREATMENT OF FOLLICULAR LYMPHOMAS

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SAŽETAK

Uvod: Folikularni limfomi su najčešći indolentni limfomi, a terapija je indicirana kod bolesnika sa simptomima ili uznapredovalim stadijumom bolesti. Citopenije kod ovih bolesnika su posledica infiltracije koštane srži ili mijelotoksičnosti terapije, a mogu predstavljati ograničavajući faktor u terapiji.

Cilj: Analiza laboratorijskih i kliničkih parametara bolesnika lečenih sa obinutuzumab -citostatskim protokolima.

Metode: Sprovedena je retrospektivna analiza podataka prikupljenih iz istorija bolesti bolesnika. Podaci su obrađeni metodama deskriptivne statistike.

Rezultati: Na Klinici za hematologiju, u periodu od 2020. do 2024. godine, je 12 bolesnika primilo obinutuzumab u sklopu antilimfomskog protokola, prosečne starosti 55. godina. Jedan bolesnik je primio predviđeni protokol u propisanom vremenskom intervalu, dok je kod 11 bolesnika došlo do odlaganja primene terapije. Dužina odlaganja terapije je varirala od 2 do 36 dana. Najčešći uzrok odlaganja terapije je bila neutropenija gr 3/4 kod 10 bolesnika (83%), od kojih su svi primali filgastrim, a 6 od neutropeničnih bolesnika (60%) je antibiotski lečeno zbog infekcije. Citopenije koje su zahtevale supstituciju derivatima krvi su bila zastupljene kod 2 bolesnika (17%). Dva bolesnika su primila transfuziju eritrocita, a jedna bolesnica i supstituciju trombocitima. Bolničko lečenje je bilo neophodno ukupno kod 3 bolesnika. Nuspojave, uključujući citopenije nisu zahtevale promenu niti obustavu primene terapije.

Zaključak: Citopenije, na prvom mestu neutropenija gradusa 2/3 utiču na ritam primene terapije, a time verovatno i na ishod lečenja. Potrebno je dugoročno praćenje ovih bolesnika radi utvrđivanja dužine preživljavanja bez progresije.

Ključne reči: citopenije, obinutuzumab, folikularni limfom

ABSTRACT

Introduction: Follicular lymphomas are the most common indolent lymphomas. Cytopenia in these patients is a consequence of bone marrow infiltration or myelotoxicity of therapy, and may represent a limiting factor in therapy.

Objective: Analysis of laboratory and clinical parameters of patients treated with obinutuzumab -cytostatic protocols.

Methods: A retrospective analysis of data collected from the patient's medical history was conducted. The data were processed using the methods of descriptive statistics.

Results: At the Hematology Clinic, in the period 2020–2024, 12 patients received obinutuzumab as part of the anti-lymphoma protocol, with an average age of 55. Only 1 patient received the therapy in rhythm, in 11 patients there was a delay in the application of the therapy. The length of treatment delay varied from 2 to 36 days. The most common cause of treatment delay was neutropenia gr 3/4 in 10 patients (83%), all of whom received filgastrim, and 6 of the neutropenic patients (60%) were treated with antibiotics for infection. Cytopenias that required substitution with blood derivatives were present in 2 patients (17%). Two patients received erythrocyte transfusion, and one patient also received platelet substitution. Hospital treatment was necessary in 3 patients. Side effects, including cytopenias, did not require a change or discontinuation of therapy.

Conclusion: Cytopenias, primarily grade 2/3 neutropenia, affect the rhythm of therapy administration, and thus probably the outcome of treatment. Long-term follow-up of these patients is needed to determine the length of progression-free survival.

Keywords: cytopenia, obinutuzumab, follicular lymphoma

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PRIMARY TESTICULAR DIFFUSE LARGE B-CELL LYMPHOMA WITH BRAIN METASTASES, A THERAPEUTIC CHALLENGE IN THE NINTH DECADE

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SAŽETAK

Uvod: Primarni testikularni limfom čini 1–2% od svih ne-Hoćkinovih limfoma, najučestaliji histološki tip je difuzni B krupnoćelijski limfom (DBKL). On je agresivna forma sa incidencom od 0,09–0,26 slučaja na 100 000.

Prikaz slučaja: Bolesnik star 82 godine jula 2022. godine imao je pad, ali ne odlazi lekaru. Nema druge bolesti, imao je operaciju prostate. Bolovao Covid 19 infekciju i vakcinisan u tri doze. Avgusta 2022. godine zbog otečenog i bolnog levog testisa javlja se urologu, urađena orhiektomia i patohistološkom analizom utvrđen DBKL (NOS). Čekajući nalaz bolesnik postaje pospan sa glavoboljama uz kognitivne smetnje. Po prispeću nalaza javlja se hematologu, postavljena je dg: DBKL CS IV AE / testis cum meta in cerebri bilateralis / IPI scor-3, ECOG-1. Promene u CNS –u bilateralno promera 3,5 cm x 3,0 cm. Primenjen je jedan ciklus imunochemoterapije (RCHOP mini), a potom metotreksat (3 g/m²) uz komplikacije febrilne neutropenije, stomatitisa i dijarealnog sindroma. Potom još tri ciklusa RCHOP mini. Na proceni odgovora verifikuje se plućna embolija, po stabilizaciji stanja primenjeno je još dva ciklusa RCOP, potom je sprovedena radioterapija u 20 seansi kontralateralno. Procena odgovora – kompletna remisija.

Zaključak: Limfom testis je redak, a posebno se retko viđa u devetoj deceniji i to sa metastazama u mozgu, a lečenje je poseban izazov.

Ključne reči: difuzni B krupnoćelijski limfom, testis, metastaze, CNS

ABSTRACT

Introduction: Primary testicular lymphoma accounts for 1–2% of all non-Hodgkin lymphoma, the most common histological type is diffuse large B-cell lymphoma (DLBCL). It is an aggressive form with an estimated incidence of 0.09–0.26 cases per 100,000.

Case report: An 82-year-old patient experiences a fall in July, 2022, but did not a visit to his physician. He denies any other illnesses, except for the prostate surgery. He was infected with COVID-19 and received three doses of vaccine. In August, 2022 he visited his urologist, due to pain and swelling in his left testicle. Orchiectomy was performed and the pathohistological confirmed DLBCL (NOS). While waiting for the results, the patient seems to get sleepy and starts having a headache followed by cognitive disturbances. Upon receiving the results, he is referred to a hematologist. Diagnosis was established: DLBCL CS IV AE / testis cum meta in cerebri bilateralis / IPI score-3, ECOG-1. The CNS changes which are present bilaterally is 3.5 cm x 3.0 cm. One cycle of immunochemotherapy (R-mini-CHOP) was administered, followed by methotrexate (3 g/m²), leading to the following complications: febrile neutropenia, stomatitis and diarrheal disease. Afterwards, three cycles R-mini-CHOP were administered. Assessment of the patient's response verified the pulmonary embolism. After stabilisation he received two more cycles R-COP, followed by 20 radiotherapy sessions contralaterally. Assessment of the response demonstrated a complete remission.

Conclusion: Testicular lymphoma is a rare malignancy and it is extremely rare in adults with brain metastases who are in the ninth decade. Its treatment presents a special challenge.

Keywords: diffuse large B-cell lymphoma, testicle, metastases, CNS

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EPIDEMIOLOŠKE I KLINIČKE KARAKTERISTIKE BOLESNIKA SA NE-HOČKINOVIM FOLIKULARNIM LIMFOMOM I UČINAK 1. LINIJE TERAPIJE – ISKUSTVA JEDNOG CENTRA

EPIDEMIOLOGICAL AND CLINICAL PROFILE OF NON-HODGKIN FOLLICULAR LYMPHOMA AND RESPONSE TO FIRST-LINE THERAPY: A SINGLE-CENTER EXPERIENCE

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SAŽETAK

Uvod: Folikularni limfom je najčešći indolentni limfom. Standard prve linije terapije mogu biti R-CHOP ili O-CHOP. U literaturi se beleži povoljan odgovor na oba protokola u više od 80% slučajeva.

Cilj: Cilj ovog rada bio je da prikaže epidemiološko-kliničke karakteristike obolelih od folikularnog limfoma i učinak prve linije terapije.

Metode: Prikupljeni su retrospektivni podaci o obolelima od folikularnog limfoma korišćenjem Registra za hronične limfoproliferativne bolesti naše Klinike za period od septembra 2022. do maja 2024. godine. Za obradu podataka korišćena je deskriptivna statistička analiza u SPSS 15.0 programu.

Rezultati: Ukupan broj bolesnika bio je 21. Prosečna starost bila je 54 (32–72), pri čemu je 57% bilo ženskog pola. U uznapredovalom kliničkom stadijumu bilo je 65% bolesnika, pri čemu je 24% imalo bulky masu na prezentaciji, 34% B simptoma, a 9% ektranodalnu lokalizaciju. Visok Flapi skor zabeležen je kod 42%, intermedijarni 29%, a nizak 29% bolesnika. Watch and wait pristup primenjen je kod 9% bolesnika, dok su ostali u prvoj liniji lečeni R-CHOP (43%) ili O-CHOP (48%) protokolom uz terapiju održavanja. Lečeni sa R-CHOP ostvarili su kompletnu remisiju u 57%, parcijalnu remisiju u 29%, odnosno progresiju u 14% slučajeva. Lečeni po O-CHOP postigli su kompletnu remisiju u 25%, parcijalnu remisiju u 62%, odnosno progresiju u 13% slučajeva.

Zaključak: Ova studija iz realne kliničke prakse naše Klinike pokazala je povoljan odgovor (KR i PR) kod više od 80% bolesnika, bez obzira na protokol, uz zapažanje boljeg učinka R-CHOP protokola u postizanju kompletne remisije.

Ključne reči: folikularni limfom, rituksimab, obinutuzumab

ABSTRACT

Introduction: R-CHOP and O-CHOP are standard first-line therapies for follicular lymphoma. Both protocols demonstrate favorable response rates exceeding 80%.

Objective: This study aimed to examine the epidemiological and clinical characteristics of patients with follicular lymphoma and evaluate the effectiveness of first-line therapies.

Methods: Retrospective data for this study were collected from September 2022 to May 2024 using the Registry for Chronic Lymphoproliferative Diseases at our institution. Descriptive statistical analysis was performed using SPSS version 15.0 software.

Results: The study included 21 patients with a mean age of 54 years (range, 32–72 years). The majority of patients were female (57%). At presentation, 65% of patients presented with advanced clinical stage disease, with 24% exhibiting bulky disease, 34% experiencing B symptoms, and 9% demonstrating extranodal involvement. FLIPI scores were distributed as follows: high 42%, intermediate 29% and low 29%. A watch-and-wait approach was adopted for 9% of patients. The remaining patients received first-line therapy with either R-CHOP (43%) or O-CHOP (48%) protocol. Among patients treated with R-CHOP, 57% achieved partial remission and 14% experienced disease progression. In the O-CHOP treatment group, 25% achieved complete remission, 62% achieved partial remission and 13% experienced disease progression.

Conclusion: In this single-center study, first-line therapy with either R-CHOP or O-CHOP resulted in a favorable response (complete remission or partial remission) in over 80% of patients. While both protocols demonstrated efficacy, the R-CHOP regime was associated with a higher rate of complete remission.

Keywords: follicular lymphoma, rituximab, obinutuzumab

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INFUSION-RELATED REACTIONS TO RITUXIMAB BIOSIMILARS IN PATIENTS WITH CHRONIC B-LYMPHOPROLIFERATIVE DISORDERS: SINGLE CENTER EXPERIENCE

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SAŽETAK

Uvod: Infuzione reakcije (IR) predstavljaju česte komplikacije primene rituksimaba, koje se uglavnom uspešno prevazilaze. U literaturi nismo pronašli poređenje različitih biosimilara rituksimaba u pogledu IR.

Cilj: Sagledati različite aspekte IR na biosimilare rituksimaba, Rixathon® i Blitzima® kojima su lečeni pacijenti sa hroničnim B-limfoproliferativnim bolestima (hBLPB) na Klinici za hematologiju UKCS 2020–2022. godine.

Metode: Iz medicinske dokumentacije su izdvojeni podaci 200 konsekutivnih pacijenata sa hBLPB koji su lečeni imunohemioterapijom u našoj ustanovi. Svi pacijenti su primili standardnu premedikaciju pre primene rituksimaba.

Rezultati: IR su se manifestovale kod 24% pacijenata. Učestalost IR nije bila povezana sa polom, starosnom dobi, stadijumom, lokalizacijom (nodalna/ekstranodalna), B simptomima, „bulky“ masom, performans statusom, tipom hemioterapije (HT) koja je primenjivana uz rituksimab niti sa vremenom primene rituksimaba u odnosu na ciklus HT (od I ciklusa vs. od II+ ciklusa). Pacijenti sa difuznim B krupnoćelijskim limfomom (DBKL) su ispoljili značajno manji broj IRR u poređenju sa drugima ($p = 0,033$), u prvom redu hroničnom limfocitnom leukemijom (15% vs. 34%; $p = 0,045$). Oni koji su lečeni u drugoj ili kasnijim terapijskim linijama češće su imali IR ($p = 0,0233$).

Zaključak: Nije uočena značajna razlika u učestalosti IR između različitih biosimilara. Pacijenti sa DBKL i oni koji su primali rituksimab u prvoj liniji, ređe su ispoljili IR u odnosu na pacijente sa drugim tipovima hBLPB, odnosno lečene u drugoj ili kasnijim linijama. Incidenca IR kod pacijenata koji su primali različite vrste biosimilara rituksimaba nije se značajno razlikovala. Arterijska hipertenzija, dijabetes melitus, koronarna bolest i pušenje nisu uticali na incidencu IR.

Cljučne reči: infuzione reakcije, hronične B-limfoproliferativne bolesti, biosimilari rituksimaba

ABSTRACT

Introduction: Infusion-related reactions (IRRs) represent frequent, although manageable complications of rituximab administration. To the best of our knowledge, no comparisons between different biosimilars in this setting have been published to date.

Objective: To assess different aspects of IRRs to rituximab biosimilars Rixathon® and Blitzima® administered to patients with chronic B-lymphoproliferative disorders (cBLPDs) treated at Clinic for Hematology, UCCS, from 2020 to 2022.

Methods: We assessed medical records of 200 consecutive patients with cBLPDs treated at our institution with immunochemotherapy in regard to clinical features and IRR occurrence. All patients received standard premedication before rituximab administration.

Results: IRRs manifested in 24% of all patients. IRR rate was not associated with gender, age, stage, disease localization (extranodal/nodal), “B” symptoms, bulky mass, performance status, type of chemotherapy adjunct to rituximab, or rituximab timing (from 1st cycle vs. from 2nd + cycle). Patients with DLBCL exhibited significantly fewer IRRs compared to others ($p = 0.033$), CLL in the first place (15% vs. 34%, respectively; $p = 0.045$). Patients treated in 2nd or later therapeutic lines more frequently exhibited IRR, compared to patients treated in 1st treatment line ($p = 0.0233$). Incidence of IRR in patients receiving different rituximab biosimilars was similar. Arterial hypertension, diabetes mellitus, coronary artery disease, and smoking did not influence IRR occurrence.

Conclusion: No difference in IRR rates between studied biosimilars was observed. DLBCL patients and patients receiving rituximab in 1st treatment line suffered from IRRs less frequently than patients with other cBLPDs and those treated in 2nd+ line, respectively.

Keywords: infusion-related reactions, chronic B-lymphoproliferative disorders, rituximab biosimilars

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ACQUIRED ANGIOEDEMA AS THE FIRST MANIFESTATION OF LYMPHOPROLIFERATIVE DISEASE

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SAŽETAK

Uvod: Hereditarni angioedema je po život opasno stanje koje dovodi do submukoznog ili subkutanog oticanja a uzrokovano je mutacijom gena za C1inhibitor komplementa. U stečenom angioedemu nastaju antitela protiv C1 inhibitora, idiopatski ili u sklopu limfoproliferativne bolesti.

Cilj: Prikazati klinički tok našeg bolesnika

Metod: Podaci su dobijeni iz medicinske dokumentacije

Rezultati: Bolesnici je 2019. godine (u pedesetoj godini) nakon više epizoda angioedema i subokluzivnih smetnji sa crevima, dijagnostikovao hereditarni angioedem. Nivo C4 < 0,05, C1 inh 0,05, funkcionalnu aktivnost nije moguće odrediti, normalan C1q. Inicijalna dijagnostika bez maligniteta ili druge autoimune bolesti. Maja 2022. lečena COVID-19 pneumonija. Od tada postoji leukocitoza sa limfocitozom, leukociti oko $17 \times 10^9/L$ uz progresivnu anemiju. Novembra 2022. na CT pregledu slezina je 193 mm, bez limfadenopatije uz B simptomatologiju. U koštanoj srži 30% nodularna infiltracija tumorskim ćelijama imunohistochemijski pozitivne na: CD20, Pax5, bcl-2 a negativne na CD3, CD5, bcl-6, CD10, CD23, Cyclin D1, CD43, odgovara spleničnom limfomu marginalne zone. Ordinirana 4 ciklusa CHOP protokola posle čega u koštanoj srži nema limfomske infiltracije, laboratorijske analize i CT uredni, kao i nivo C1 inh, C1q, C3, C4, hemolizna aktivnost klasičnim i alternativnim putem, funkcionalna aktivnost C1 inhibitora.

Zaključak: Stečeni angioedem se viđa kod low grade limfoma, spleničnog marginalne zone i nekada godinama prethoditi pojavi limfoma.

Ključne reči: stečeni angioedem, splenični limfom marginalne zone, prikaz slučaja

ABSTRACT

Introduction: Hereditary angioedema is a life-threatening condition that leads to submucosal or subcutaneous swelling and is caused by a mutation in the complement C1 inhibitor gene. In acquired angioedema, antibodies against C1 inhibitors are produced, idiopathically or as part of a lymphoproliferative disease.

Objective: To show the clinical course of our patient

Methods: Data were obtained from medical records

Results: The patient was diagnosed with hereditary angioedema in 2019 (at the age of 50) after several episodes of angioedema and subocclusive problems with the intestines. C4 level < 0.05, C1 inh 0.05, functional activity cannot be determined, normal C1q. Initial diagnosis without malignancy or other autoimmune disease. May 2022, treated for COVID-19 pneumonia. Since then, there has been leukocytosis with lymphocytosis, leukocytes around $17 \times 10^9/L$ with progressive anemia. In November 2022, on a CT scan, the spleen was 193 mm, without lymphadenopathy with B symptoms. In the bone marrow, 30% nodular infiltration with tumor cells immunohistochemically positive for: CD20, Pax5, bcl-2 and negative for CD3, CD5, bcl-6, CD10, CD23, Cyclin D1, CD43 corresponds to marginal zone splenic lymphoma. Prescribed 4 cycles of the CHOP protocol, after which there is no lymphoma infiltration in the bone marrow, laboratory analyzes and CT are normal, as well as the level of C1 inh, C1q, C3, C4, hemolytic activity by classical and alternative pathways, functional activity of C1 inhibitors.

Conclusion: Acquired angioedema is seen in low grade lymphoma, splenic marginal zone and sometimes years before the appearance of lymphoma.

Keywords: acquired angioedema, marginal zone splenic lymphoma, case report

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PRIMARY CNS LYMPHOMA (PCNSL) TREATED WITH MATRIX REGIMEN FOLLOWED BY HIGH-DOSE CONSOLIDATION: A CASE REPORT

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SAŽETAK

Uvod: PCNSL predstavlja izazov u kliničkoj praksi uzimajući u obzir nepovoljne karakteristike bolesti, kao i toksičnost agresivnijih modaliteta lečenja. Kod mlađih/fit pacijenata preporučen je pristup intenzivne indukcije uz visokodoznu konsolidaciju sa autolognim graftom.

Cilj: prikazati tok lečenja pacijenta sa PCNSL koji je tretiran MATRIX režimom.

Prikaz slučaja: Pacijent starosti 33 godine bez komorbiditeta i porodičnog opterećenja operisan je na Klinici za neurohirurgiju UKC Niš usled centralne simptomatologije i MR verifikovane ekspanzivne promene. Patohistološki potvrđen PCNSL (DBKL). Postoperativni MR endokranijuma bio je bez znakova za rest tumora. Pacijent je stadiran kao I E CS, IELSG score 0. Lečenje je započeto indukcionim režimom MATRIX (rituksimab 375 mg/m² d0, HD MTX 3,5 g/m² d1, HD AraC 2 g/m²/12h d2-d3, tiotepa 30 mg/m² d4). Intenzivna bikarbonatna hidracija praćena leukovorinskom podrškom rezultirala je brzom ekskrecijom MTX-a. Postterapijski tok proticao je uz razvoj aplazione krize, ali je samo u ciklusu 3 zabeležena febrilna neutropenija. Ordinirano je ukupno 4 ciklusa. Redukcija doze AraC načinjena je od 3. ciklusa (-1 aplikacija). Nakon svake terapije sprovedena je primarna G-CSF i antibiotska profilaksa (aciklovir, Bactrim, flukonazol, ciprofloksacin). Evaluacioni MR endokranijuma bio je bez znakova rest/recidiva. Potom je sprovedena visokodozna konsolidacija sa autolognom potporom. Posttransplantacioni period protiče uz protrahovanu citopeniju bez značajnijih komplikacija.

Zaključak: Primena MATRIX režima sa visokodoznom konsolidacijom standard je lečenja mlađih/fit pacijenata. Značajna, ali titrabilna hematološka toksičnost je glavi neželjeni efekat tretmana.

Ključne reči: primarni CNS limfom, MATRIX režim, prikaz slučaja

ABSTRACT

Introduction: PCNSL represents a significant clinical challenge considering its unfavourable characteristics and the toxicity of aggressive treatment modalities. In younger/fit patients dose intensity induction with autologous graft is the recommended approach.

Case report: Here we present a 33-year-old male patient without comorbidities and a family history of malignancies who was administered at the neurosurgery department due to neurological symptoms and MRI verified brain tumour. Extirpation was performed and the pathology report confirmed the PCNSL (DL-BCL) diagnosis. Postoperative MRI showed no signs of disease and the patient was staged as CS IE, PS ECOG 0 with an IELSG score of 0. Induction was initiated using a MATRIX regimen (rituximab 375 mg/m² d0, HD MTX 3.5 g/m² d1, HD AraC 2 g/m²/12h d2-d3, thiotepa 30 mg/m² d4). Each cycle was accompanied by intensified hydration and leucovorin support with its titration depending on the MTX level. Each cycle was followed by G-CSF support and antiviral and antibiotic prophylaxis (aciklovir, Bactrim, fluconazole, ciprofloxacin). In total 4 cycles were administered with each cycle followed by high-grade haematological toxicity, with febrile neutropenia after the third cycle which led to the reduction of Ara-C dosing (-1 application). Post-therapeutic MRI showed no signs of disease and subsequently, high-dose consolidation with autologous graft was performed. Protracted cytopenia is registered in post-transplant period but without any significant complications.

Conclusion: MATRIX regimen with high-dose consolidation represents a standard of care in young/fit patients with PCNSL. Haematological toxicity as a main adverse event represents a clinical challenge which is manageable.

Keywords: primary CNS lymphoma, MATRIX regimen, case report

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PROGNOSTIC SIGNIFICANCE OF BCL-2 EXPRESSION IN NON-GERMINAL CENTER B-CELL-LIKE DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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SAŽETAK

Uvod: Prognostički značaj ekspresije bcl2 proteina u DBKL prilagođenog Hans klasifikatoru višestruko je ispitivan sa kontradiktornim rezultatima.

Cilj: Utvrditi nezavistan i IPI prilagođen prognostički značaj ekspresije bcl2 proteina u non-GCB DBKL.

Metode: Sproveli smo retrospektivnu analizu 97 pacijenata sa non-GCB DBKL tretiranih Rituksimab-om+ CHOP/CHOP slični režimi na Klinici za onkologiju UKC Niš u periodu 2008–2023. Prebojenost > 50% neoplastičnih ćelija (DAKO klon 124) smatrana je cut off vrednošću za bcl2 pozitivnost. Bilo je (n = 70; 72,2%) bcl2 pozitivnih pacijenata. Karakteristike pacijenata na osnovu bcl2 ekspresije komparirane su primenom χ^2 i Student-ovog t-testa. Posmatran je ukupni terapijski odgovor (ORR), a ukupni 5-PFS i 5-OS procenjavani su Kaplan-Majerovom analizom. Upoređivanje pacijenata sa ili bez ekspresije bcl2 i prilagođavanje IPI skoru vršeno je primenom log-rank testa (CI 95%; $p < 0,05$).

Rezultati: U odnosu na bcl2 pozitivnost nije bilo signifikantnih razlika po starosti ($p = 0,28$), polu ($p = 0,35$), prisustvu „bulky” mase ($p = 0,6$), nivou LDH ($p = 0,14$), lokalizaciji ($p = 0,63$), kliničkom stadijumu ($p = 0,97$), IPI skoru ($p = 0,81$). Pacijenti su predominantno tretirani R-CHOP režimom (78,2%). Preostalih (23,8%) primalo je DA-EPOCH-R, R-CHOEP, R-CVP, R-HD MTX. Nije bilo signifikantne razlike u ORR u odnosu na bcl2 ekspresiju (81,5% vs. 77,6%, $p = 0,92$). Ukupni 5-PFS i 5-OS bio je nesigantan ($p = 0,81$; $p = 0,59$), respektivno. U analizi prilagođavanja sa IPI skorom (IPI 0-1 vs IPI 2), nije zabeležena signifikantnost u 5-PFS i 5-OS ($p = 0,56$; $p = 0,59$), respektivno. Zabeležen je trend nepovoljnog 5-OS u IPI ≥ 2 grupi nezavisno od bcl2 ekspresije.

Zaključak: Bcl2 pozitivnost nema nezavistan, niti IPI prilagođen prognostički značaj u non-GCB DBKL.

Cljučne reči: non-GCB DBKL, bcl2 protein, prognoza

ABSTRACT

Introduction: The prognostic value of bcl-2 expression in DLBCL adjusted with Hans classifier was vastly explored with contradictory results.

Objective: To assess independently and IPI adjusted prognostic value of bcl-2 expression in non-GCB DLBCL.

Methods: A retrospective analysis of 97 non-GCB DLBCL patients was conducted at Oncology Clinic UCC Niš treated with Rituximab + CHOP/CHOP-like from 2008–2023. Bcl-2 positive finding was considered if > 50% neoplastic cells (DAKO clone 124) were stained. Seventy (72.2%) patients were bcl-2 positive. χ^2 or Student's t-test was used to compare patient's bcl-2 status. The overall response rate (ORR) was observed, while Kaplan-Meier method was used to assess 5-PFS, and 5-OS. Log-rank test was used to compare patients with/ without bcl-2 expression and for IPI score adjustment (CI 95%; $p < 0.05$).

Results: Regarding bcl-2 positivity no statistical significance was observed based on age ($p = 0.28$), gender ($p = 0.35$), "bulky" mass ($p = 0.6$), LDH (0.14), site ($p = 0.63$), clinical stage ($p = 0.97$), IPI ($p = 0.84$). Patients were predominantly treated with R-CHOP regimen (78.2%). While other (23.8%) received DA-EPOCH-R, R-CHOEP, R-CVP, R-HD MTX. There were no difference in ORR based on bcl-2 status (81.5% vs. 77.6%; $p = 0.92$). No significant difference was observed in 5-PFS, and 5-OS ($p = 0.81$; $p = 0.59$), respectively. When the data were adjusted with IPI score (IPI 0-1 vs. IPI ≥ 2), no significant difference in 5-PFS, and 5-OS ($p = 0.56$; $p = 0.59$), were found. Overall, unfavorable trend was seen in IPI ≥ 2 subgroup, independently of bcl-2 status.

Conclusion: Bcl2 positivity has no independent, nor IPI-adjusted prognostic significance in non-GCB DLBCL.

Keywords: non-GCB, bcl-2 protein, prognosis

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POLATUZUMAB-VEDOTIN+BENDAMUSTIN+RITUXIMAB U RELAPS/REFRAKTARNOM DIFUZNOM B KRUPNOĆELIJSKOM LIMFOMU (R/R DBKL) – STUDIJA SERIJE SLUČAJA JEDNOG CENTRA

POLATUZUMAB-VEDOTIN+BENDAMUSTIN+RITUXIMAB IN RELAPS/REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA (R/R DLBCL): SINGLE INSTITUTION EXPERIENCE

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SAŽETAK

Uvod: R/R DBKL predstavlja klinički izazov. Rezultati studije faze II sa polatuzumab-vedotinom+bendamustin+rituximab (PolaBR) pokazali su povoljne rezultate kod 40% tretiranih. Prikazujemo 6 slučajeva lečenih u našoj ustanovi.

Cilj: Odrediti efikasnost i bezbednost PolaBR "salvage" terapije u našoj populaciji pacijenata.

Metode: Na Klinici za onkologiju UKC Niš tretirano je 6 R/R DBKL pacijenata PolaBR-om, u periodu oktobar 2021. – jun 2024. godine. Bilo je 4 pacijenta muškog pola (67%) i 2 ženskog (33%), prosečne starosti 58,3 godine (43–67), svi povoljnog ECOG performans statusa (0–1). Polovina pacijenta bilo je u IV kliničkom stadijumu, uz elevirane vrednosti LDH i prisustvo „bulky” mase na prezentaciji. Ekstranodalna formu imalo je 4 pacijenta (želudac kod dvoje, slezina i tonzila), ostala 2 imali su nodalni oblik bolesti. Efikasnost je procenjena kroz ukupnu stopu odgovora (ORR) i stopu kontrole bolesti (DCR) korišćenjem PET/CT-a, dok je toksičnost procenjena korišćenjem kriterijuma (CTCAE v5.0).

Rezultati: PET/CT-om verifikovan je ORR kod njih 5, dok je DCR postignuta kod svih pacijenata. Kod 3 pacijenta postignuta je kompletna remisija (CR), od kojih je kod jednog sprovedena visokodозна konsolidacija sa autolognom potporom. Dva pacijenta preminula su tokom tretmana, jedan usled komplikacija HCV+ ciroze jetre a drugi od, najverovatnije, septičkih komplikacija. Zabeleženi su hematološki neželjeni efekti kod svih lečenih, od čega neutropenija gradusa 3–4 kod 4 pacijenta (66%), koji su zahtevali G-CSF kao sekundarnu profilaksu.

Zaključak: PolaBR se pokazao kao moćan „salvage” tretman u R/R DBKL. Hematološki neželjeni efekti mogu biti visokog gradusa s toga preporučujemo primenu primarne profilakse G-CSF-om.

Ključne reči: R/R DBKL, polatuzumab-vedotin, serija slučajeva

ABSTRACT

Introduction: R/R DLBCL represents a clinical challenge. Phase II trials exploring polatuzumab-vedotin+rituximab-bendamustin (PolaBR) was beneficial in 40% of treated patients. We present our single institution experience with 6 patients.

Objective: To assess the efficacy and safety of PolaBR "salvage" treatment in our patient population.

Methods: A total of 6 patients were treated with PolaBR at Oncology Clinic UCC Niš from October 2021 – June 2024. There were 4 males (67%) and 2 females (33%) patients, mean age 58.3 years (43–67), all with favorable ECOG performance status (0–1). Half of the patients were in the IV clinical stage, with elevated LDH and "bulky" mass at presentation. Extranodal form was verified in 4 patients (stomach in two, spleen and tonsil), the other 2 had a nodal form of the disease. Efficacy was assessed through overall response rate (ORR) and disease control rate (DCR) by using PET/CT, while toxicity was scored using the (CTCAE v5.0) criteria.

Results: ORR was verified by PET/CT in 5 patients, while all patients had DCR. Complete remission (CR) was achieved in 3 patients, one of whom underwent high-dose consolidation with autologous support. Two patients died during the treatment, one due to complications of HCV+ liver cirrhosis and the other from, most likely, septic complications. Hematological adverse events were recorded in all patients with grade 3–4 neutropenia in 4 patients (66%) requiring secondary prophylaxis with G-CSF.

Conclusion: PolaBR represents a powerful salvage, often accompanied by high-grade haematological toxicity, therefore primary prophylaxis with G-CSF is recommended.

Keywords: R/R DLBCL, polatuzumab-vedotin, case series

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ABO BLOOD GROUP AND RISK OF VENOUS THROMBOEMBOLISM IN DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS

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SAŽETAK

Uvod: Venska tromboembolija (VTE) je česta komplikacija kod pacijenata sa agresivnim limfomom. Ranije je opservirana povezanost između krvne grupe i razvoja VTE.

Cilj: Cilj istraživanja bio da analizira da li ABO krvna grupa predstavlja faktor rizika za razvoj VTE kod pacijenata sa difuznim B-krupnoćelijskim limfomom (DBKL).

Metode: Ovo je bicentrična studija koja je obuhvatila 448 pacijenata sa dijagnozom DBKL koji su regrutovani iz dva centra: Klinike za hematologiju, Univerzitetskog kliničkog centra Srbije i sa Hematologije, Odeljenja za translacionu i preciznu medicinu, Univerziteta Sapienza u Rimu, Italija. Podaci o događajima VTE prikupljeni su za sve pacijente uključene u studiju od trenutka postavljanja dijagnoze do 3 meseca nakon poslednjeg ciklusa terapije.

Rezultati: Medijana starosti pacijenata bila je 59 godina, a 55,8% su bili muškarci. Stopa VTE je bila 11,8% (53 pacijenta). VTE je dijagnostikovana pre početka hematološkog lečenja kod 54,7% pacijenata sa DBKL, dok je kod 45,3% pacijenata VTE dijagnostikovana nakon otpočinjanja hematološkog lečenja. Nije uočena značajna povezanost između razvoja VTE i tipa ABO grupe ($p = 0,122$). Stopa VTE kod DBKL pacijenata sa A krvnom grupom bila je 3,8%, kod B 2,7%, kod AB 1,8%, a kod O 3,6%. Nije primećena značajna razlika između ABO grupa i vremena razvoja VTE ($p = 0,122$).

Zaključak: U ovoj proširenoj bicentričnoj kohorti pacijenata sa DBKL, nismo uočili povezanost između ABO krvne grupe i razvoja VTE. Za potvrdu ovog nalaza, potrebno je dalje istraživanje

Ključne reči: VTE, DBKL, ABO krvna grupa

ABSTRACT

Introduction: Venous thromboembolism (VTE) is a frequent complication in aggressive lymphoma patients. The relation between blood group type and VTE occurrence has been observed earlier.

Objective: The study aimed to analyze if ABO blood represents a risk factor for VTE development in patients with diffuse large B-cell lymphoma (DLBCL).

Methods: This is a bicentric study that has included 448 patients with DLBCL that have been recruited from two centers: Clinic for Hematology, University Clinical Center of Serbia, and from Hematology, Department of Translational and Precision Medicine, Sapienza University of Rome, Italy. Data regarding VTE events were collected for all the patients included in the study from the time of diagnosis to 3 months after the last cycle of therapy.

Results: The median patients' age was 59, and 55.8% were males. The rate of VTE was 11.8% (53 patients). VTE was diagnosed before the initiation of hematological treatment in 54.7% of DLBCL patients, while 45.3% of DLBCL patients were diagnosed with VTE after the initiation of hematological treatment. We have not found a significant association between VTE development and ABO group type ($p = 0.122$). The rate of VTE in DLBCL patients with A blood type was 3.8%, in B 2.7%, in AB 1.8%, and in O 3.6%, respectively. No significant difference between the ABO groups and the time of VTE development has been observed ($p = 0.122$).

Conclusion: In this extended bicentric cohort of DLBCL patients, we have not found an association between DLBCL patients' blood group and VTE development.

Keywords: VTE, DLBCL, ABO blood group

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THE SIGNIFICANCE OF PROGNOSTIC INDICES IN MANAGING FOLLICULAR LYMPHOMA: VALIDATION THROUGH NEURAL NETWORK

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SAŽETAK

Uvod: Prognošički indeksi (IPI, FLIPI i FLIPI2) doprinose efikasnom upravljanju folikularnim limfomom i drugim vrstama ne-Hoćkinovih limfoma.

Cilj: Cilj je bio potvrditi rezultate istraživanja tradicionalnim pristupom kroz treniranje neuronske mreže, gde su ulazi FLIPI skorovi pacijenata u grupi visokog rizika, a izlaz terapija.

Metode: Istraživanje je sprovedeno na 257 pacijenata sa folikularnim limfomom. Svi pacijenti su, prema IPI, FLIPI i FLIPI2 faktorima, svrstani u grupu niskog, srednjeg i visokog rizika. Korišćene su metode kliničkog i hematološkog pregleda i statistička obrada i analiza. Neuronska mreža je trenirana sa FLIPI skorovima kao ulazima za grupu visokog rizika, za predikciju izbora terapije.

Rezultati: Radijaciona terapija je primenjena kod pacijenata u svim prognošičkim grupama. Strategija „watch and wait“ korišćena je za pacijente sa niskim i visokim rizikom prema FLIPI, te niskim i srednjim prema FLIPI2. Hemioterapija i imunohemioterapija su primenjene kod svih prognošičkih grupa. Imunoterapija je korišćena kod pacijenata kod svih grupa prema ostalim indeksima, a splenektomija i transplantacija matičnih ćelija su primenjene kod 5 (1,95%). Kompletna remisija postignuta je kod 85 (33,07%).

Zaključak: Najveći broj (19,84%) svrstan je u grupu visokog rizika na osnovu FLIPI indeksa. FLIPI2 nije svrstao veći broj pacijenata u grupu visokog rizika. Validacija rezultata neuronskom mrežom pokazala je robusnost ovih indeksa u izboru terapije.

Ključne reči: folikularni limfom, FLIPI, terapija, neuronska mreža

ABSTRACT

Introduction: Prognostic indices (IPI, FLIPI, and FLIPI2) contribute to effective management of follicular lymphoma and other types of non-Hodgkin lymphomas.

Objective: The study aimed to validate research results traditionally and through training a neural network, with FLIPI scores of patients in high-risk group as inputs and therapy as output.

Methods: The study included 257 patients with follicular lymphoma. All patients were categorized into low, intermediate, and high-risk groups based on IPI, FLIPI, and FLIPI2 factors. Clinical and hematological examination methods, as well as statistical processing and analysis, were used. A neural network was trained with FLIPI scores as inputs for the high-risk group to predict treatment selection.

Results: Radiation therapy was administered to patients in all prognostic groups. The “watch and wait” strategy was used for patients with low and high risk by FLIPI, and low and intermediate risk by FLIPI2. Chemotherapy and immunotherapy were applied across all prognostic groups. Immunotherapy was used for patients all other index groups, splenectomy and stem cell transplantation were performed in 5 (1.95%) patients. Complete remission was achieved in 85 (33.07%) patients.

Conclusion: The majority (19.84%) were classified as high-risk based on the FLIPI index. FLIPI2 did not classify a larger number of patients into the high-risk group. Validation of results through a neural network demonstrated the robustness of these indices in therapy selection.

Keywords: follicular lymphoma, FLIPI, therapy, neural network

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ANALYSIS OF LABORATORY PARAMETERS IN PATIENTS WITH NEWLY DIAGNOSED FOLLICULAR LYMPHOMA (FL) AND THEIR IMPACT ON DISEASE COURSE – FIVE-YEAR SINGLE CENTRE EXPERIENCE UCC KRAGUJEVAC

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SAŽETAK

Uvod: Ne-Hoćkinovi limfomi indolentnog toka, među kojima je i folikularni limfom, predstavljaju posebnu grupu limfoproliferativnih bolesti koji i pored toga što po klasifikaciji pripadaju malignim bolestima pokazuju hroničan tok. Iako retko, ova bolest može pokazati agresivnost, sklonost ka komplikacijama, ali i rezistentnost na primenjivanu terapiju i česte relapse.

Cilj: je analizirati laboratorijske parametre pacijenata pri dijagnozi i njihovu povezanost sa ishodom bolesti, komplikacijama, terapijskim odgovorom i preživljavanjem.

Metode: Analizirano je 47 pacijenata kod kojih u periodu od 2018 – januara 2024. godine postavljena dijagnoza folikularnog limfoma. Analizirani su parametri krvne slike (broj leukocita, leukocitarna formula, hemoglobin, broj trombocita), parametri hemostaze (PT, apTT, fibrinogen, d dimer) kao i biohemijski parametri (urea, kreatinin, jonogram, hepatogram, LDH, ac. uricum).

Rezultati: Parametri krvne slike kao i većina biohemijskih parametara nisu pokazali korelaciju sa tokom bolesti. Kompletanu remisiju postizali su pacijenti koji su imali niže vrednosti d dimera ($p = 0,034$), niži nivo fibrinogena ($p = 0,035$) kao i niže vrednosti LDH ($p = 0,014$), dok je sveukupno preživljavanje bilo duže kod pacijenata sa nižim vrednostima fibrinogena ($p = 0,037$), višim procentom monocita ($p = 0,009$) i višim procentom bazofila ($p = 0,035$). Na preživljavanje bez bolesti uticali su niži nivo fibrinogena ($p = 0,018$) i niži nivo d dimera ($p = 0,024$). Pacijenti sa inicijalno povišenim vrednostima d dimera imali su PFS $24,50 \pm 4,81$ meseci, dok su oni sa d dimerom u granicama referentnih vrednosti imali PFS $36,48 \pm 5,99$ ($p = 0,015$).

Zaključak: U iskustvu našeg centra parametri hemostaze, fibrinogen i d dimer pokazali su značajnu korelaciju sa tokom bolesti.

Ključne reči: folikularni limfom, fibrinogen, d dimer, tok bolesti

ABSTRACT

Introduction: Indolent non-Hodgkin lymphomas (NHL), in which follicular lymphoma, present a group of malignant lymphoproliferative diseases with chronic course. Though rarely, course can be aggressive, fullfilled with complications but also therapy refractory and relapsing.

Objective: of the paper was to analyse laboratory parameters of patient at diagnosis and their relation to disease outcome, complications, therapy response as well as OS and PFS

Methods: Group consisted of 47 patients diagnosed in the period of 2018–2024. Parameters analysed were CBC (leukocyte number, hemoglobin, leukocyte formula, platelet number), hemostatic parameters (PT, aPTT, fibrinogen, d dimer), and biochemical parameters (urea, creatinin, electrolytes, transaminases, LDH, uric acid).

Results: Parameters of CBC likewise most of biochemical parameters showed no impact to disease course. Complete remissions were more likely in the patients with lower d dimer concentration ($p = 0.034$), lower fibrinogen level ($p = 0.035$) as well as lower concentration of LDH ($p = 0.014$), while overall survival (OS) was longer in patients with lower fibrinogen concentration ($p = 0.037$), higher monocyte percentage ($p = 0.009$) and higher basophil percentage ($p = 0.035$). Progression free survival (PFS) was longer in patients with lower fibrinogen concentration ($p = 0.018$) and lower d dimer concentration ($p = 0.024$). Patients with initially high d dimer concentration had PFS 24.50 ± 4.81 months, while those whose d dimer level was normal had PFS 36.48 ± 5.99 months. ($p = 0.015$)

Conclusion: In our, single centre experience hemostatic parameters, fibrinogen and d dimer showed significant impact on disease course.

Keywords: follicular lymphoma, fibrinogen, d dimer, disease course

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ANALYSES OF TREATMENT RESULTS FOR PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA AT UNIVERSITY HOSPITAL MEDICAL CENTER BEZANIJSKA KOSA IN THE ERA OF IMMUNOCHEMOTHERAPY

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SAŽETAK

Uvod: Difuzni veliki B-ćelijski limfom (DLBCL) je agresivna bolest sa varijabilnim kliničkim, histološkim, imunofenotipskim i citogenetskim karakteristikama i promenljivom prognozom. Stoga su potrebni precizni prognostički alati za identifikaciju kliničkih i bioloških parametara koji predviđaju terapijski odgovor i omogućavaju dizajniranje individualizovane terapije u DLBCL.

Cilj: Ova studija je urađena u cilju utvrđivanja rezultata lečenja bolesnika sa DLBCL, prognostičkih faktora i ishoda lečenja u ispitivanoj grupi bolesnika.

Metode: U studiju je uključeno 314 bolesnika sa DLBCL koji su lečeni u KBC „Bežanijska kosa” u eri primene rituksimaba, u periodu od 2008. do 2024. godine. Analizirane su kliničke i laboratorijske karakteristike, terapijski odgovor, prognostički faktori i preživljavanje bolesnika.

Rezultati: U ispitivanoj grupi bolesnika bilo je 153 (48,7%) muškarca i 161 (51,3%) žena. Od ukupnog broja praćenih pacijenata, 181 (57,5%) je bilo starije od 60 godina. 159 (52%) bolesnika je bilo u uznapredovalom kliničkom stadijumu bolesti. 172 (55,6%) bolesnika je imalo visok ili visok/intermedijaran NCCN-IPI. 172 (65,62%) bolesnika su bili nonGCB podtipa. Ukupan terapijski odgovor je bio 82,8%. U momentu zaključenja studije bilo je živo 179 (57%) bolesnika. Utvrđena je značajna razlika u preživljavanju bolesnika u odnosu na životnu dob, ECOG, vrednosti hemoglobina, LDH, albumina, CRP, beta2mikroglobulina, IPI i NCCN-IPI. Nezavisni prognostički parametri bili su životna dob i NCCN-IPI. Medijana preživljavanja je iznosila 110 meseci.

Zaključak: Izlečenje kod bolesnika sa DLBCL je postignuto kod više od polovine bolesnika. Faktori koji su najviše uticali na ishod kod naših bolesnika su životna dob i NCCN-IPI. Rezultati lečenja naših pacijenata su u saglasnosti sa rezultatima lečenja bolesnika sa DBKL iz literature.

Ključne reči: difuzni B-krupnoćelijski limfom, imunohemioterapija, prognostički faktori, preživljavanje

ABSTRACT

Introduction: Diffuse Large B-Cell Lymphoma (DLBCL) is a highly aggressive disease with diverse clinical, histological, immunophenotypic, and cytogenetic features, leading to variable prognoses. Accurate prognostic tools are crucial for predicting therapeutic responses and tailoring individualized treatments.

Objective: This study aimed to assess treatment outcomes for DLBCL patients, identify prognostic factors, and evaluate treatment efficacy.

Methods: The study involved 314 DLBCL patients treated at University Hospital Medical Center Bezanijska kosa from 2008 to 2024, during the rituximab era. Clinical and laboratory data, therapeutic responses, prognostic factors, and patient survival were analyzed.

Results: Among the patients, 153 (48.7%) were men and 161 (51.3%) were women, with 181 (57.5%) over 60 years old. Advanced disease was present in 159 (52%) patients, and 172 (55.6%) had high or high/intermediate NCCN-IPI scores. The majority, 172 (65.62%), had the non-GCB subtype. The overall therapeutic response rate was 82.8%, and 179 (57%) patients were alive at the study's conclusion. Significant survival differences were associated with age, ECOG performance status, hemoglobin levels, LDH, albumin, CRP, beta2-microglobulin, IPI, and NCCN-IPI. Age and NCCN-IPI were identified as independent prognostic factors. The median overall survival was 110 months.

Conclusion: More than half of the DLBCL patients achieved cure, with age and NCCN-IPI being the most influential factors on outcomes. These findings align with existing literature on DLBCL treatment results.

Keywords: diffuse large b-cell lymphoma, immunochemotherapy, prognostic factors, survival rate

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ANALYSIS OF THERAPY RESPONSE IN THE FIRST LINE THERAPY IN
THE TREATMENT OF FOLLICULAR LYMPHOMA – FIVE-YEAR FOLLOW
UP, EXPERIENCE OF UNIVERSITY CLINICAL CENTER KRAGUJEVAC

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SAŽETAK

Uvod: Folikularni limfom predstavlja drugi limfom po učestalosti limfoidnih maligniteta u Evropi. Odlikuje se uglavnom indolentnim tokom i dugogodišnjim preživljavanjem, ali ne treba zanemariti potencijal ka transformaciji u agresivne oblike. Imunohemioterapija u prvoj liniji lečenja folikularnog limfoma doprinela je kako boljem inicijalnom terapijskom odgovoru, tako i ukupnom preživljavanju pacijenata.

Cilj: Uporediti terapijski odgovor prve terapijske linije kod pacijenata obolelih od folikularnog limfoma.

Metode: Analizirano je 47 pacijenata koji u periodu od 2018–2024. godine lečeni pod dijagnozom folikularnog limfoma u prvoj terapijskoj liniji primenom protokola R-C(H)OP ili O-C(H)OP. Analizirane su demografske karakteristike pacijenata, komorbiditeti, parametri proširenosti bolesti, patohistološki gradus, prognostni parametri, parametri krvne slike i biohemijski parametri, kao i odgovor pacijenata na primenjenu terapiju, sveukupno preživljavanje i preživljavanje do ponovne pojave bolesti ili transformacije.

Rezultati: U navedenim grupama nije bilo detektovane razlike u demografskim karakteristikama, komorbiditetima, prognostnim parametrima kao ni parametrima bolesti. U grupi pacijenata koji su primali rituksimab u terapiji detektovana je veća učestalost postizanja kompletne remisije u odnosu na grupu pacijenata koja primala obinutuzumab ($p < 0,01$), dok su ukupno preživljavanje i preživljavanje bez progresije bolesti bile bez razlika među grupama.

Zaključak: U iskustvu našeg centra na malom uzorku, u prvoj terapijskoj liniji lečenja folikularnog limfoma protokoli bazirani na rituksimabu pokazuju bolji efekat u postizanju kompletne remisije u odnosu na protokole bazirane na obinutuzumabu, ali bez razlike preživljavanju.

Ključne reči: folikularni limfom, imunohemioterapija, procena odgovora

ABSTRACT

Introduction: Follicular lymphoma is the second most common lymphoma in Europe. It is characterized by a mostly indolent course and long-term survival, but the potential for transformation into aggressive forms should not be ignored. Immunochemotherapy in the first line of follicular lymphoma treatment contributed both to a better initial therapeutic response and to overall patient survival.

Objective: To compare the therapeutic response of the first line therapy in patients with follicular lymphoma (FL).

Methods: Group of 47 patients who were treated in the period from 2018 to 2024 under the diagnosis of follicular lymphoma in the first line therapy were divided in to groups: one group received RC(H)OP protocol, and other group received OC(H)OP protocol. Demographic characteristics of patients, comorbidities, disease parameters, pathohistological grade, prognostic parameters, blood count parameters and biochemical parameters, as well as patient response to applied therapy, overall survival and progression free survival were analyzed.

Results: There were no detected differences in demographic characteristics, comorbidities, prognostic parameters and disease parameters in the mentioned groups. In the group of patients who received rituximab in therapy, a higher frequency of achieving complete remission was detected compared to the group of patients who received obinutuzumab ($p < 0.01$), while OS and PFS were similar between the groups.

Conclusion: In the experience of our center on a small sample, in the first line treatment of follicular lymphoma protocols based on rituximab show a better effect in achieving complete remission compared to protocols based on obinutuzumab, but with no difference in survival.

Keywords: follicular lymphoma, immunochemotherapy, response assessment

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EPIDEMIOLOGICAL AND CLINICAL CHARACTERISTICS OF PATIENTS WITH DIFFUSE B LARGE CELL LYMPHOMA AND RESPONSE TO FIRST LINE THERAPY – EXPERIENCE OF OUR CENTER

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SAŽETAK

Uvod: Difuzni B krupnoćelijski limfom (DBKL) najčešća je ne-Hoćkinova limfomska neoplazma.

Cilj: Prikaz iskustva Klinike za hematologiju UKC Niš sa obolelima od DBKL, njihovih epidemioloških, kliničkih karakteristika i ishoda lećenja.

Metode: Retrospektivna analiza istorija bolesti 83 pacijenta sa DBKL lećenih na Klinici za hematologiju UKC Niš upisanih u Registar za hronične limfoproliferativne bolesti od septembra 2022. do maja 2024. godine. Korišćene su metode deskriptivne statistike.

Rezultati: Medijana starosti pri postavljanju dijagnoze je bila 61 (22–87), ženskog pola 55,42%, ECOG < 2 75,90%, Bulky masom na prezentaciji 30,12%, ektranodalnom lokalizacijom 54,21% bolesnika. Prema Ann Arbor klasifikaciji: I CS 33,73%, II 20,48%, III 13,25%, IV 32,53%. Nespecifični tip imalo je 85,54% bolesnika, primarni medijastinalni B krupnoćelijski limfom (PMBKL) 12,04%, jedan bolesnik High grade B limfom (HGBL), jedan primarni limfom CNS-a. Bolesnici sa nespecifičnim tipom lećeni su u prvoj liniji RCHOP protokolom 74,64%, ostali drugim terapijskim modalitetima. PMBKL 7/10 pacijenata lećeno je R-DA-EPOCH, 3/10 RCHOP protokolom, limfom CNS-a MATRIX protokolom, pacijent sa HGBL R-DA-EPOCH protokolom. Odgovor nakon prve linije kod nespecifičnog tipa: CR = 72%, PR = 7%, SD = 7%, PD = 14%, odnosi se na pacijente kojima je načinjena procena (43/71), dok je kod 24 pacijenta terapija u toku, četvoro je egzitalo. Odgovor kod PMBKL: CR = 30%, PR = 20%, SD = 10%, PD = 10%, terapija u toku kod 30%. Pacijent sa HGBL je progredirao, a pacijent sa limfomom CNS-a je imao CR.

Zaključak: Nakon prve terapijske linije CR postiglo je 62,75%. Izazov je prepoznati pacijente kandidate za nove terapijske opcije kojima će se postići bolji ishodi lećenja.

Ključne reči: limfom, DBKL, ishod

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ABSTRACT

Introduction: Diffuse B large cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma neoplasm.

Objective: Presentation of the experience of the Clinic of Hematology the University Hospital of Niš with patients with DLBCL.

Methods: Retrospective analysis of the medical history of 83 patients with DLBCL treated at the Hematology Clinic registered in the Registry for Chronic Lymphoproliferative Diseases from September 2022 to May 2024. Descriptive statistics methods were used.

Results: At the diagnosis median age was 61 (22–87), female gender 55.42%, ECOG < 2 75.90%, Bulky mass 30.12%, extranodal localization in 54.21% patients. Ann Arbor classification: I CS 33.73%, II 20.48%, III 13.25%, IV 32.53%. 85.54% had a non-specific type, primary mediastinal B large cell lymphoma (PMBLCL) 12.04%, one patient with High-grade B-cell lymphoma (HGBL), one with primary CNS lymphoma. 74.64% patients with a non-specific type were treated in the first line with the RCHOP, the rest with other therapeutic modalities. PMBLCL 7/10 patients were treated with R-DA-EPOCH, 3/10 with RCHOP, CNS lymphoma with MATRIX, HGBL with R-DA-EPOCH protocol. The response in the non-specific type: CR = 72%, PR = 7%, SD = 7%, PD = 14%, refers to patients who were evaluated (43/71), ongoing therapy in 24, four died. Response in PMBLCL: CR = 30%, PR = 20%, SD = 10%, PD = 10%, ongoing therapy in 30%. The patient with HGBL progressed, the patient with CNS lymphoma had a CR.

Conclusion: After the first line of therapy, CR was achieved in 62.75%. The challenge is to recognize patients who are candidates for new therapeutic options that will achieve better treatment outcomes.

Keywords: lymphoma, DLBCL, outcome

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ARTERIAL THROMBOSIS AS RARE COMPLICATION IN NON-HODGKIN LYMPHOMA PATIENT

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SAŽETAK

Uvod: Manifestacije venske tromboze (VTE) povezane sa kancerom su dobro poznat pojam, o čemu govore i brojni skorovi rizika za razvoj VTE kod pacijenata sa limfomom. Ipak, malo je studija koje govore u prilog arterijskih tromboemboliziranih događaja (ATE) kod pacijenata sa hematološkim malignitetima.

Prikaz slučaja: Sedamdesetogodišnja pacijentkinja javila se u Urgentni centar usled jakih, probadajućih bolova u levoj potkolenici. Bolovi su se javili deset dana po početku prvog ciklusa hemoterapije koja je podrazumevala primenu cisplatine, citarabina i deksametazona u sklopu lečenja refraktarnog difuznog B-krupnoćelijskog ne-Hoćkinovog limfoma. Kliničkim pregledom ustanovljeno je da je leva noga hladna, sa oštećenom motoričkom i senzornom funkcijom, uz gotovo nepalpabilan puls a. dorsalis pedis. Laboratorijski nalazi su pokazali blagu normocitnu anemiju, trombocitopeniju, povišen C-reaktivni protein. Jedini faktor rizika koji je pacijentkinja imala bila je hiperholesterolemija. CT angiografija je potvrdila akutnu ishemiju usled masivne tromboze leve arterije femoralis superficialis, od njenog početka do a. cruralis, sa a. tibialis posterior kao jedinom protočnom.

Zaključak: Studije ukazuju na incidencu ATE od 8,3–9,1% kod hemoterapije bazirane na cisplatini, dok gojaznost, pušenje i dislipidemija dodatno povećavaju rizik. Iako postoje brojne skale rizika koje predviđaju VTE kod pacijenata sa limfomom (npr. ThroLy skor), odgovarajući model za predviđanje ATE kod hematoloških maligniteta još ne postoji. Prognostički, pacijenti sa aktivnim malignitetom i ATE imaju stopu mortaliteta i do 80% tokom godinu dana. Prevencija uključuje primenu aspirina, pažljiv izbor hemoterapije, vodeći računa o komorbiditetima kao što su dijabetes i hipertenzija. Usmerenost pažnje na trombotske rizike tokom lečenja karcinoma je od suštinskog značaja.

Ključne reči: limfomi, DBKL, arterijske tromboze, tromboze povezane sa kancerom cancer-associated thrombosis

ABSTRACT

Introduction: Venous manifestations of cancer-associated thrombosis is well established and there are several risk scores specifically predict VTE in lymphoma patients. Literature on preventing and treating arterial thromboembolism (ATE) in hematological cancer patients is limited.

Case report: A 70-year-old woman presented to the Emergency Department with severe, stabbing pain in her left lower leg, appearing ten days into her first cycle of cisplatin, cytarabine, and dexamethasone chemotherapy for recurrent diffuse large B-cell non-Hodgkin lymphoma. Clinical examination revealed her left leg and foot were unusually cold, with a faint pulse in the left dorsalis pedis artery and impaired motor and sensory functions. Laboratory results showed mild normocytic anemia, thrombocytopenia, elevated C-reactive protein. Her only identifiable risk factor appeared to be hypercholesterolemia. CT angiography confirmed acute ischemia due to extensive thrombosis in the left superficial femoral artery, obstructing it from origin to crural arteries, with the posterior tibial artery as the sole outflow.

Conclusion: Studies indicate an 8.3–9.1% ATE incidence with cisplatin-based chemotherapy, exacerbated by factors like obesity, smoking, and dyslipidemia. Chemotherapy-induced endothelial damage, microvascular changes, and inflammatory cytokines contribute to a prothrombotic state. Although several risk scores specifically predict VTE in lymphoma patients (e.g., ThroLy score), a corresponding model for predicting ATE in hematological malignancies does not yet exist. The prognosis for patients grappling with both active malignancy and ATE is dire, with an 80% one-year mortality rate even after specific surgical interventions. Preventative strategies include aspirin, careful chemotherapy selection, and managing comorbidities like diabetes and hypertension. Vigilance for thrombotic risks during cancer treatment is paramount.

Keywords: lymphoma, cancer-associated thrombosis, arterial thrombosis, DLBCL

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TREATMENT OF A PATIENT WITH A LATE RELAPSE OF DLBCL LYMPHOMA INELIGIBLE FOR SCT – CASE REPORT

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SAŽETAK

Uvod: Oko 40% pacijenata sa difuznim B-krupnoćelijskim limfomom (DLBCL) ima refraktornu bolest ili recidiv nakon prve linije liječenja. Posljednjih godina odobreno je nekoliko novih terapija koje pružaju efikasnije opcije od konvencionalne hemoterapije uz zadovoljavajući profil toksičnosti. Obećavajući su rezultati liječenja novim modalitetom liječenja polatuzumab vedotinom u kombinaciji sa rituksimabom i bendamustinom (pola-RB).

Prikaz slučaja: Predstavljamo vam pacijenta starog 74 godine. Riječ je o pacijentu kod kojeg je 2006. godine postavljena dijagnoza ne-Hoćkinovog limfoma – DLBCL. Tada tretiran sa osam ciklusa po R-CHOP uz postizanje remisije bolesti. U aprilu 2023. godine zbog bolova u krsnom dijelu leđa je sprovedena radiološka obrada. Na MSCT abdomena se verifikuje tu masa u retroperitonemu 85x65 mm. Urađen je PET CT kojim se u abdomenu uočava hipermetabolička masa (75x102 mm, SUVmax 35,2) u abdomenu. Urađena je biopsija retroperitonealne mase (FNB „fine needle biopsy“). Pristigli patohistološki nalaz je ukazao na relaps bolesti. Pacijent stejdžiran kao NHL CS IVB (ph: DLBCL – CGB tip), IPI score 4, ECOG 1. Odlučeno da se sprovede liječenje po pola-RB protokolu. Primijenjeno je 6 ciklusa liječenja uz postizanje remisije, bez značajnijih toksičnih efekata terapije.

Zaključak: Polatuzumab vedotin je anti-CD79b antitijelo konjugovano sa monometil auristatinom E koje je u navedenoj kombinaciji pokazalo značajnu kliničku aktivnost za pacijente sa relapsom/refraktornim DLBCL.

Ključne reči: DLBCL, polatuzumab vedotin, liječenje

ABSTRACT

Introduction: About 40% of patients with diffuse large B-cell lymphoma (DLBCL) have refractory disease or relapse after first-line treatment. In recent years, several new therapies have been approved that provide more effective options than conventional chemotherapy and that have a satisfactory toxicity profile. The results of treatment with new treatment modalities such as polatuzumab vedotin in combination with rituximab and bendamustine (pola-RB) are promising.

Case report: We present to you a 74-year-old patient. This is a patient who was diagnosed with Non-Hodgkin lymphoma - DLBCL in 2006. He was then treated with eight cycles of R-CHOP, achieving disease remission. In April 2023, radiological treatment was carried out due to pain in the lumbar region of the back. MSCT of the abdomen verifies that mass in the retroperitoneum 85x65 mm. A PET CT scan was performed, which revealed a hypermetabolic mass (75x102 mm, SUVmax 35.2) in the abdomen. A biopsy of the retroperitoneal mass (FNB “fine needle biopsy”) was performed. The received pathohistological findings indicated a relapse of the underlying disease. The patient was staged as NHL CS IVB (ph: DLBCL – CGB type), IPI score 4, ECOG 1. It was decided to carry out the treatment according to the Pola-R-Bendamustine protocol. 6 cycles of treatment were applied, achieving remission, without significant toxic effects of the therapy.

Conclusion: Polatuzumab vedotin is an anti-CD79b antibody conjugated with monomethyl auristatin E which in the above combination showed significant clinical activity for patients with relapsed/refractory DLBCL.

Keywords: DLBCL, polatuzumab vedotin, treatment

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PROGNOSTIC SIGNIFICANCE OF CRP-ALBUMIN-LYMPHOCYTE (CALLY) INDEX IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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SAŽETAK

Uvod: Difuzni B-krupnoćelijski limfom (DBKL) ostaje neizlečiva bolest kod trećine bolesnika i pored primene savremene ciljane terapije. Uz molekularne, intenzivno se istražuju novi neinvazivni klinički prognostički parametri koji bi pomogli u identifikovanju podgrupe visokorizičnih bolesnika. C-reaktivni protein-albumin-limfocitni (CALLY) indeks se pokazao korisnim i prediktivnim u stratifikaciji bolesnika sa karcinomima, ali još nije ispitivan kod obolelih od DBKL.

Cilj: Poređenje vrednosti CALLY indeksa kod novodijagnostikovanih bolesnika sa DBKL sa postojećim i prihvaćenim laboratorijskim i kliničkim prognostičkim parametrima, kao i sa odgovorom na prvu terapijsku liniju, ishodom i preživljavanjem.

Metode: Retrospektivnom studijom obuhvaćena su 183 uzastopna bolesnika sa DBKL (muškarci: 77/183 (42,1%); prosečna starost: 67 godina, raspon 22–91) koji su dijagnostikovani i lečeni u tri Kliničko-bolnička centra: KBC „Zemun“, KBC „Bežanijska kosa“ i KBC „Zvezdara“. CALLY indeks je računat po formuli: (albumin x apsolutni broj limfocita) / (CRP x 104).

Rezultati: Granična (cut-off) vrednost CALLY indeksa 1,2 određena je statističkom analizom. Visoke vrednosti CALLY indeksa ($\geq 1,2$) su bile povezane sa povišenom LDH ($p < 0,001$) i beta-2 mikroglobulinom ($p < 0,001$), uznapredovalim kliničkim stadijumom ($p = 0,004$), kao i sa visokim IPI ($p < 0,001$) i aalPI ($p < 0,001$), lošim R-IPI ($p < 0,001$). Nije bilo razlike u odnosu na podtip DBKL (GCB vs. ABC), ektranodalnom prezentacijom, ekspresijom CD10 i CD5. Bolesnici sa niskim CALLY indeksom ($< 1,2$) su imali značajno bolji odgovor na prvu terapijsku liniju ($p < 0,001$), nižu stopu mortaliteta ($p < 0,001$) i značajno duže preživljavanje (28 vs. 46 meseci, $p < 0,001$).

Zaključak: Naša iskustva ukazuju da CALLY indeks može predstavljati nov, nezavisan, lak za izvođenje i pouzdan klinički prognostički indeks u identifikaciji visokorizičnih bolesnika sa DBKL.

Ključne reči: difuzni B-krupnoćelijski limfom, CALLY indeks, prognostički značaj

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ABSTRACT

Introduction: Diffuse large B-cell lymphoma (DLBCL) remains incurable in 30–40% of patients despite targeted treatment. There is an increased need to obtain easy-to-perform and widely applicable non-invasive clinical biomarkers for identifying subgroups of high-risk patients. The C-reactive protein-albumin-lymphocyte (CALLY) index has been recently introduced as a useful and sensitive predictive tool for stratification in cancers, but has not been comprehensively evaluated in DLBCL.

Objective: We aimed to evaluate the correlation of the CALLY index in newly diagnosed DLBCL patients with established laboratory and clinical prognostic parameters, response to treatment, outcome, and survival.

Methods: We retrospectively analyzed the medical records of 183 consecutive patients with DLBCL (males 77/183 (42.1%); median age 67 years, range 22–91) diagnosed and treated at three University Clinical Hospital Centers – CHC Zemun, CHC Bežanijska kosa and CHC Zvezdara. CALLY index was defined as (Albumin $\times$ Lymphocyte) / (CRP $\times$ 104).

Results: The cut-off value of the CALLY index was determined at 1.2. CALLY Index ≥ 1.2 was associated with elevated LDH ($p < 0.001$) and beta-2 microglobulin levels ($p < 0.001$), advanced clinical stage ($p = 0.004$), as well as high IPI ($p < 0.001$) and aalPI ($p < 0.001$), poor R-IPI ($p < 0.001$). There were no differences regarding DLBCL subtype (GCB vs. ABC), extranodal presentation, CD10, and CD5 expression. Patients with low CALLY had significantly better response to first-line treatment ($p < 0.001$), lower mortality rate ($p < 0.001$), and better overall survival (28 vs. 46 months, $p < 0.001$).

Conclusion: The CALLY index may be an independent and significant indicator of poor outcomes in patients with DLBCL.

Keywords: diffuse large B-cell lymphoma, CALLY index, prognostic significance

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MONOMORPHIC EPITHELIOTROPIC INTESTINAL T-CELL LYMPHOMA (MEITL) – A RARE ENTITY

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SAŽETAK

Uvod: MEITL je ekstremno raritetan nodalni oblik T/NK ćelijskog limfoma. Karakteriše ga visoka agresivnost i tendencija ka relapsu, kao i kratko 5-godišnje preživljavanje (< 20%).

Cilj: prikazati kliničke karakteristike i ishod lečenja bolesnika sa MEITL.

Prikaz slučaja: Pacijent starosti 59 godina iz Vranja, inicijalno se prezentovao slikom akutnog abdomena u formi ileusa te je hitno operisan u OB Vranje. Tada je načinjena resekcija jejunuma sa makroskopskom verifikacijom infiltrativnog tumora. U Centru za patologiju UKC Niš potvrđen je T/NK ćelijski limfom tipa MEITL, sa sledstvenim imunofenotipom: CD3+, CD8+, CD56+, bcl2+, Granzyme B+, Ki67 80%. Na klinici za onkologiju UKC Niš načinjeno je stadiranje bolesti (MSCT skenovi celog tela, biopsija srži, virusološki, imunološki skrining i krvne analize). Jedini patološki supstrat bio je nalaz obostranih plućnih infiltrata. Pacijent je stadiran kao IV CS, A, a, IPI-2, povoljnog performans statusa (ECOG 0) sa dobro regulisanim DM2 kao komorbiditetom. Sprovedena je intenzivna indukcija po režimu CHOEP14 (ciklofosfamid, doksorubicin, vinkristin, etopozid, prednizon) u 8 ciklusa sa primarnom G-CSF i antibiotskom profilaksom (aciklovir, trimetoprim/sulfametoksazol). Visokogradusna hematološka toksičnost bila je prisutna, bez razvoja febrilne neutropenije i infektivnih komplikacija. Na kraju indukcije postiže se vrlo dobra parcijalna remisija (vgPR) kao odgovor. Pacijent je dalje prosleđen na visokodoznu konsolidaciju sa autolognim graftom.

Zaključak: Režim „dozne gustine“ CHOEP14 uz visokodoznu konsolidaciju prvog povoljnog odgovora trenutno predstavlja optimalan pristup u lečenju MEITL sa ograničenim benefitom. Neantraciklinski režimi pokazali su superiornost, mada ih aktuelni NCCN vodič nije podržao. CHOEP14 relativno je bezbedan režim uz obaveznu G-CSF i antibiotsku profilaksu.

Ključne reči: MEITL, CHOEP14, autologna konsolidacija

ABSTRACT

Introduction: MEITL represents a rare form of nodal T/NK-cell lymphoma characterized by a low 5-year survival rate (< 20%) due to its aggressiveness and high relapse rate.

Case report: Here we present a 59-year-old male who was admitted at the surgical ward with clinical presentation of ileus. Intraoperatively, an infiltrative tumor was observed, thus jejunum resection was performed. The pathology report confirmed T/NK cell lymphoma – MEITL with a characteristic immunophenotype CD3+, CD8+, CD56+, bcl2+, Granzyme B+, Ki67 80%. At the Oncology Clinic, University Clinical Center Niš staging was conducted (whole-body CT scans, bone marrow biopsy, virology, immunology, complete blood work). Bilateral lung infiltration was the only aberrant finding. The patient was staged as CS IV, A, a, IPI-2 with performance status of ECOG 0, and only well controlled type 2 diabetes as comorbidity which was with oral antidiabetics. Intensified induction was initiated with CHOEP14 regimen (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisolone) with G-CSF, and antimicrobial prophylaxis (aciklovir, Bactrim). In total 8 cycles were administered with the occurrence of high-grade haematological toxicity (without febrile neutropenia or infective complications). Post-therapeutic scans showed vgPR, and subsequently, the patient was directed to a high-dose consolidation with autologous graft.

Conclusion: Dose density CHOEP14 with high dose consolidation after the first favourable response represents a plausible approach in patients with MEITL, although with limited success. Non-anthracycline regimens showed superiority, although not supported by NCCN guidelines yet. Even though CHOEP14 represents an aggressive regimen, with adequate prophylaxis it can be administered safely.

Keywords: MEITL, CHOEP14, autologous consolidation

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A CASE OF EXTENSIVE FACIAL BONE OSTEOMYELITIS DURING TREATMENT WITH RITUXIMAB MAINTENANCE FOR RECURRENT FOLLICULAR LYMPHOMA

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SAŽETAK

Uvod: Folikularni limfom (FL) je indolentna neizlečiva bolest heterogenog toka. Terapija održavanja rituksimabom sada predstavlja standardnu terapiju nakon završetka imunohemioterapije sa rituksimabom. Mi prezentujemo slučaj pacijentkinje sa rekurentnim FL koja je razvila osteomijelitis tokom terapije održavanja rituksimabom.

Prikaz slučaja: Pacijentkinja stara 64 godina sa uznapredovalim folikularnim limfomom gradusa II lečena je intenzivnom hemoterapijom (R-CHOP, R-DHAP) i autologom transplantacijom matičnih ćelija hematopoeze u svojoj 59 godini zbog refraktarnog FL. Postignuta je parcijalna remisija. Međutim, godinu i po dana kasnije, kod pacijentkinje je registrovan relaps bolesti, takođe u uznapredovalo fazi ali sa manjom tumorskom masom. Nakon nekoliko ciklusa imunohemioterapije sa rituksimabom (R-FC), kod pacijentkinje je započeta terapija održavanja rituksimabom. Mesec dana po završetku terapije, pacijentkinja se javlja zbog febrilnosti i bola u usnoj duplji. Učinjena je kompjuterizovana tomografija koja je pokazala osteolitične lezije maksile i tvrdog nepca sa patološkom komunikacijom između usne i nosne duplje. Biopsija promene potvrdila je osteomijelitis izazvan *Pseudomonas* spp. Ekstenzivna nekrektomija i antimikrobna terapija, uz uspešnu sekundarnu rekonstrukciju oralne i nazalne šupljine sanirale su promene kod pacijentkinje.

Zaključak: Rituksimab može izazvati osteomijelitis zahvaćene kosti kao rezultat imunosupresije usled deplecije B ćelija. Osteomijelitis izazvan rituksimabom može biti saniran ekstenzivnom hitnom nekrektomijom zahvaćene kosti.

Ključne reči: folikularni limfom, imunohemioterapija sa rituksimabom, imunosupresija, osteomijelitis

ABSTRACT

Introduction: Follicular lymphoma (FL) is an incurable indolent disease with a heterogeneous course. Rituximab maintenance (RM) is now the standard choice after rituximab-based immunochemotherapy. Here, we report the case of a patient with recurrent FL who developed osteomyelitis during the treatment with RM.

Case presentation: A 64-year-old woman with advanced stage follicular lymphoma grade II underwent intensive chemotherapy (R-CHOP, R-DHAP) and autologous stem cell transplantation at age 59 due to treatment refractory FL. Partial remission was achieved. But, one and half year later, she experienced relapse of FL, also in advanced stage but with less tumor burden. After several cycles of rituximab-based therapy (R-FC), RM was administered. One month after treatment completion, the patient visited our clinic because of continuous fever and painful oral cavity. A computed tomography scan showed an osteolytic change in the maxillar bone and hard palate with pathological communication between oral and nasal cavity. Biopsy was performed, which indicated facial bone osteomyelitis caused by *Pseudomonas* spp. Extensive debridement and antimicrobial therapy followed by secondary reconstruction of the oral and nasal cavity was successfully performed.

Conclusions: Rituximab may cause osteomyelitis of the affected bone as a result of immunosuppression due to B-cell depletion. Rituximab-induced osteomyelitis may be manageable by extensive debridement performed without delay.

Keywords: follicular lymphoma, rituximab-based immunochemotherapy, immunosuppression, osteomyelitis

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HOČKINOV LIMFOM

HODGKIN LYMPHOMA

POREĐENJE A-HIPI MODELA I KLASIČNOG IPS SKORA KOD NOVODIJAGNOSTIKOVANIH BOLESNIKA SA UZNAPREDOVALIM STADIJUMOM HOČKINOVOG LIMFOMA

COMPARISON OF THE A-HIPI MODEL AND THE CLASSIC IPS SCORE IN NEWLY DIAGNOSED ADVANCED-STAGE HODGKIN LYMPHOMA PATIENTS

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SAŽETAK

Uvod: Poslednjih godina, sve se više dovodi u pitanje značaj IPS skora u predikciji ishoda lečenja Hoćkinovog limfoma, te je u cilju poboljšanja njegove prediktivne vrednosti osmišljena modifikacija u vidu A-HIPI modela kojim se izražava verovatnoća petogodišnjeg preživljavanja bez progresije bolesti (PFS) i ukupnog preživljavanja (OS).

Cilj: Poređenje prediktivnog značaja A-HIPI modela i klasičnog IPS skora kod bolesnika sa uznapredovalim stadijumom Hoćkinovog limfoma.

Metode: Uzorak je obuhvatio 34 bolesnika koji su dijagnostikovani u IIB, III i IV kliničkom stadijumu bolesti u periodu od 2016. do 2024. godine. Podaci su dobijeni retrospektivno, uvidom u medicinsku dokumentaciju. Za procenu prediktivne vrednosti korišćen je Harelov indeks podudarnosti (Harrell's C-index).

Rezultati: Medijana praćenja bolesnika je bila 27,5 meseci. U ovom periodu progresija bolesti je verifikovana kod 5, a smrtni ishod kod 2 bolesnika. Petogodišnji PFS i OS procenjeni na osnovu A-HIPI modela su bili 78,64% i 93,81%. Prediktivne vrednosti A-HIPI modela za PFS (C-indeks = 0,54) i OS (C-indeks = 0,33) su bile značajno niže u odnosu na prediktivnu vrednost IPS skora za PFS (C-indeks = 0,61) i OS (C-indeks = 0,78).

Zaključak: Na našem uzorku bolesnika dobijena je loša prediktivna vrednost A-HIPI modela, dok je za klasični IPS skor potvrđena umerena prediktivna vrednost za PFS i dobra prediktivna vrednost za OS. U cilju verifikacije značaja A-HIPI skoring sistema neophodan je veći broj bolesnika koji će biti praćeni u dužem vremenskom intervalu.

Cljučne reči: A-HIPI model, IPS skor, Hoćkinov limfom

ABSTRACT

Introduction: The importance of the IPS score in predicting the outcome of Hodgkin lymphoma treatment has been increasingly questioned. To improve its predictive value, the modification in the form of the A-HIPI model was designed. It expresses the probability of five-year progression-free survival (PFS) and overall survival (OS).

Objective: Comparison of the predictive significance of the A-HIPI model and the classic IPS score in patients with advanced-stage Hodgkin lymphoma.

Methods: The sample included 34 patients who were diagnosed in the advanced stage of the disease, in the period from 2016 to 2024. The data were collected retrospectively, by reviewing the medical documentation. Harrell's C-index was used to assess the predictive value of scoring systems.

Results: Median patient follow-up was 27.5 months. During that period, progression occurred in 5, and death occurred in 2 patients. Five-year PFS and OS estimated based on the A-HIPI model were 78.64% and 93.81%. The predictive values of the A-HIPI model for PFS (C-index = 0.54) and OS (C-index = 0.33) were significantly lower compared to the predictive values of IPS for PFS (C-index = 0.61) and OS (C-index = 0.78).

Conclusion: A poor predictive value of the A-HIPI model was obtained, while a moderate predictive value for PFS and a good predictive value for OS were confirmed for the classic IPS score. A larger number of patients and a longer follow-up period are necessary to verify the significance of the A-HIPI scoring system.

Keywords: A-HIPI model, IPS score, Hodgkin lymphoma

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PROGNOSTIC SIGNIFICANCE OF INFLAMMATORY MARKERS IN NEWLY DIAGNOSED HODGKIN LYMPHOMA PATIENTS

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SAŽETAK

Uvod: Procena faktora rizika u predikciji ishoda lečenja Hoćkinovog limfoma predstavlja osnovu za optimizaciju terapijskog pristupa. Hronična inflamacija ima značajnu ulogu u razvoju i progresiji malignih bolesti, te se inflamatorni markeri smatraju dobrim prediktorima terapijskog ishoda.

Cilj: Analiza inflamatornih markera kao prediktivnih faktora za dužinu preživljavanja bez progresije bolesti (PFS) i ukupnog preživljavanja (OS) kod bolesnika sa novodijagnostikovanim Hoćkinovim limfomom.

Metode: Uzorak je obuhvatio 45 bolesnika dijagnostikovanih u periodu od 2016. do 2024. godine. Podaci su dobijeni retrospektivnim uvidom u medicinsku dokumentaciju. Za obradu podataka su korišćene analiza preživljavanja i regresiona analiza.

Rezultati: Tokom navedenog perioda dijagnoza Hoćkinovog limfoma postavljena je kod 69 bolesnika. Nakon isključivanja bolesnika koji su tek započeli terapiju i bolesnika sa nepotpunom medicinskom dokumentacijom, krajnji uzorak je obuhvatio 45 bolesnika. Analizirani su sledeći faktori rizika: CRP – medijana 25,4, NLR (neutrofilno-limfocitni odnos) – medijana 5,42, PLR (trombocitno-limfocitni odnos) – medijana 255,05 i LMR (limfocitno-monocitni odnos) – medijana 1,85. Među navedenim parametrima, jedino se LMR izdvojio kao statistički značajan prediktor za PFS ($p = 0,03$), dok ni kod jednog od navedenih parametara nije dokazana statistička značajnost u predikciji OS.

Zaključak: LMR predstavlja statistički značajan prediktor za PFS kod bolesnika sa novodijagnostikovanim Hoćkinovim limfomom. Nije dokazana statistička značajnost u ostalim ispitivanim parametrima, što je verovatno posledica malog uzorka bolesnika i veće mogućnosti statističke greške, te je neophodno dalje praćenje i uključivanje većeg broja bolesnika u istraživanje, radi optimalnije procene prediktivnih faktora.

Ključne reči: Hoćkinov limfom, prognostički faktori, inflamatorni markeri

ABSTRACT

Introduction: Risk factors assessment in predicting the outcome of Hodgkin lymphoma treatment is necessary for optimizing the therapeutic approach. Chronic inflammation plays a significant role in the development and progression of malignant diseases, and inflammatory markers are considered good predictors of therapeutic outcomes.

Objective: Estimating the predictive value of inflammatory markers for progression-free survival (PFS) and overall survival (OS) in newly diagnosed Hodgkin lymphoma patients.

Methods: The sample included 45 patients diagnosed in the period from 2016 to 2024. Data were obtained by retrospective review of medical records. Survival analysis and regression analysis were used for data processing.

Results: During the follow-up period, the diagnosis was confirmed in 69 patients. After excluding patients who had just started therapy and patients with incomplete medical documentation, the final sample included 45 patients. The following risk factors were analyzed: CRP – median 25.4, NLR (neutrophil-lymphocyte ratio) – median 5.42, PLR (platelet-lymphocyte ratio) – median 255.05, and LMR (lymphocyte-monocyte ratio) – median 1.85. Among these parameters, only LMR was singled out as a statistically significant predictor of PFS ($p = 0.03$), while none of the parameters showed statistical significance of OS.

Conclusion: LMR represents a statistically significant predictor of PFS in newly diagnosed Hodgkin lymphoma patients. Statistical significance has not been proven for other examined parameters, probably due to a small sample of patients and the possibility of statistical error. Further monitoring of a larger number of patients is necessary for a more optimal assessment.

Keywords: Hodgkin lymphoma, prognostic factors, inflammatory markers

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BRENTUXIMAB VEDOTIN IN FIRST-LINE TREATMENT OF PATIENTS WITH STAGE IV HODGKIN LYMPHOMA – OUR EXPERIENCE

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SAŽETAK

Uvod: Brentuksimab vedotin (BV) je konjugat anti-CD 30 antitijela i lijeka monometil auristatin E. Pored drugih indikacija, indikovano je za liječenje adultnih pacijenata sa prethodno neliječenim Hočkinovim limfomom (HL) u 4. kliničkom stadijumu.

Cilj: Prikazati efikasnost i bezbjednost primjene BV kod pacijenata u 4. kliničkom stadijumu Hočkinovog limfoma.

Metode: Retrospektivna studija je obuhvatila šest pacijenata (pet pacijenata muškog i jedan ženskog pola), starosne dobi 19, 21, 32, 37, 50 i 82 godine. Svi pacijenti su bili sa klasičnim Hočkinovim limfomom i CD30 pozitivnošću. Tretirani su sa BV u dozi od 1,2 mg/kg u kombinaciji sa hemioterapijom (doksorubicin, vinblastin, dakarbazin) na 1. i 15. dan svakog 28-dnevnog ciklusa. Odgovor je procenjen nakon četiri ciklusa terapije po A-AVD protokolu.

Rezultati: Kod četiri pacijenta je postignuta kompletna remisija bolesti, a kod dva je terapija u toku. Osim afebrilne neutropenije blažeg stepena drugih neželjenih efekata nije bilo.

Zaključak: Brentuksimab vedotin se pokazao efikasnim i bezbjednim u liječenju pacijenata sa četvrtim kliničkim stadijumom HL.

Ključne reči: Hočkinov limfom, četvrti stadijum, brentuksimab vedotin

ABSTRACT

Introduction: Brentuximab vedotin (BV) is a conjugate of an anti-CD30 antibody and the drug monomethyl auristatin E. Among other indications, it is indicated for the treatment of adult patients with previously untreated Stage IV Hodgkin lymphoma (HL).

Objective: To present the efficacy and safety of BV in patients with stage IV Hodgkin lymphoma.

Methods: This retrospective study included six patients (five males and one female), aged 19, 21, 32, 37, 50, and 82 years. All patients had classical Hodgkin lymphoma and CD30 positivity. They were treated with BV at a dose of 1.2 mg/kg in combination with chemotherapy (doxorubicin, vinblastine, dacarbazine) on days 1 and 15 of each 28-day cycle. The response was assessed after four cycles of the A-AVD therapy protocol.

Results: Complete remission of the disease was achieved in four patients, while two are still undergoing therapy. Apart from mild afebrile neutropenia, there were no other adverse effects.

Conclusion: Brentuximab vedotin has proven to be effective and safe in the treatment of patients with Stage IV Hodgkin lymphoma.

Keywords: Hodgkin lymphoma, stage IV, brentuximab vedotin

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NIVOLUMAB IN THE TREATMENT OF HODGKIN LYMPHOMA

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SAŽETAK

Uvod: Hoćkinova bolest je lokalizovana ili proširena zloćudna proliferacija ćelija limforetikularnog sistema (Reed Sternbergovih) koja zahvata u prvom redu tkiva limfnih čvorova i koštano srž. Liječenje podrazumijeva u zavisnosti od kliničkog stadijuma, radioterapiju, hemioterapiju, transplantaciju autolognih matičnih ćelija. U uznapređovalom IV stadijumu bolesti, sa brojnim relapsima efikasnost je pokazala imunoterapija.

Prikaz slučaja: Tridesetjednogodišnjem pacijentu dijagnosticiran je Hoćkinov limfom (SN) CS IVB 2014. godine. Liječen na Klinici za Hematologiju VMA Beograd po svim terapijskim protokolima. U avgustu 2015. godine urađena autologa TMČH. Potom provedena terapija sa 16 th doza brentuksimab vedotin. U februaru 2017. godine provedena iradijacija zahvaćenih kostiju karlice i desnog femura sa 30 GY/10 frakcija. Potom primio X ciklusa th protokol LVPP, zatim vinblastin svakih 15 dana (dvije doze). Liječenje praćeno brojnim relapsima. U januaru 2019. godine u terapiju uvede nivolumab amp. u dozi 240 mg svakih 14 dana do progresije bolesti ili razvoja komplikacija. Uvedena terapija pokazala efikasnost u kliničkom, laboratorijskom i radiološkom smislu. Tokom 2020/2021. godine nastavljena aplikacija nivolumaba, u više navrata terapija odložena za 3 mjeseca zbog nemogućnosti nabavke lijeka usljed COVID-19 pandemije. Nakon četiri godine pacijent hospitalizovan zbog sumnje na relaps bolesti, koji je dijagnostičkom obradom isključen.

Zaključak: Imunoterapija nivolumabom je pokazala značajnu terapijsku aktivnost i prihvatljiv bezbjedonosni profil kod pacijenta sa prethodno teško liječenim relapsom ili refraktornim Hoćkinovim limfomom.

Ključne reči: Hoćkinova bolest, imunoterapija, nivolumab

ABSTRACT

Introduction: Hodgkin disease is a localized or extended malignant proliferation of the cells of the lymphoreticular system (Reed Sternberg's), primarily affecting the lymph nodes and bone marrow. Treatment includes radiotherapy, chemotherapy and autologous stem cell transplantation (ASCT) depending on the clinical stage. In advanced stage IV disease with multiple relapses, immunotherapy has shown effectiveness.

Case report: A 31-year-old patient was diagnosed with stage IVB Hodgkin lymphoma (SC) in 2014. He received treatment at the Hematology Clinic of the VMA Belgrade according to standard protocols. In August 2015, he underwent autologous ASCT followed by 16 doses of brentuximab vedotin. In February 2017, the affected pelvic bones and right femur were irradiated with 30 GY/10 fractions. Subsequently, he received X cycles of the LVPP protocol and vinblastine every 15 days (two doses), but continued to experience multiple relapses. In January 2019, nivolumab was introduced at a dose of 240 mg every 14 days until disease progression or complications arose. This therapy demonstrated clinical, laboratory, and radiological effectiveness. Despite delays in 2020/2021 due to the COVID-19 pandemic, nivolumab treatment was continued. After four years, the patient was hospitalized for a suspected relapse, which was ruled out by diagnostic work-up.

Conclusion: Immunotherapy with nivolumab has shown significant therapeutic activity and an acceptable safety profile in patients with previously difficult-to-treat relapsed or refractory Hodgkin lymphoma.

Keywords: Hodgkin disease, immunotherapy, nivolumab

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FIVE-YEAR ANALYSIS OF THE TREATMENT OF NEWLY DIAGNOSED PATIENTS WITH MORBUS HODGKIN – REAL CLINICAL PRACTICE

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SAŽETAK

Uvod: Morbus Hodgkin je limfoproliferativno oboljenje sa učestalošću 2–3/100 000 ljudi. Studije su pokazale da nakon prve terapijske linije po protokolu ABVD (adriablastin, bleomicin, velbe, vinblastin, dakarbazin) 80% pacijenata u uznapredovaloj bolesti postiže kompletnu remisiju (CR).

Cilj: Ciljevi rada su bili analiza uspeha lečenja novoobolelih u posmatratom petogodišnjem periodu i analiza uticaja: kliničkog stadijuma, ektranodalne lokalizacije, IPS skora i bulky bolesti na terapijski odgovor

Metode: Sprovedena je retrospektivna analiza 58 obolelih od morbus Hodgkin u periodu od 31.12.2018. do 31.12.2023. godine. Uključujući kriterijum novodijagnostikovani oboleli, podaci dobijeni iz pisane medicinske dokumentacije. Statistička analiza učinjena SPSS 22.0, značajnost je $p < 0,05$.

Rezultati: Prosečna starost 58 obolelih bila je $40,02 \pm 16,01$ godina. Prvom linijom lečenja ABVD ostvarena je kompletna remisija (CR) kod 67,2%, parcijalni odgovor kod 13,8%, a progresija bolesti u 19% bolesnika. U obolelih bez kompletne remisije posle 6 modaliteta lečenja u periodu od pet godina, kompletna remisija postignuta kod 64,5%. Od 12 mobilisanih uspešno je transplantirano 9 uz postignutu CR. Najviše ispitanika je imalo proširenu bolest 67,3% (CS IV i III). Klinički stadijum i ektranodalna bolest, nisu bili u korelaciji sa kompletnom remisijom ($p > 0,05$). IPS skor i bulky bolest su pokazali negativnu korelaciju sa postizanjem kompletne remisije ($p < 0,05$).

Zaključak: Uspeh lečenja Hočkinovog limfoma prvom linijom nije zadovoljavajući.

Ključne reči: morbus Hodgkin, ABVD, kompletna remisija (CR)

ABSTRACT

Introduction: Morbus Hodgkin represents an incidence rate of 2–3 cases per 100,000 people. Studies have shown that after the first-line therapy with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) 80% of the advanced stage patients achieve complete remission (CR).

Methods: A retrospective analysis was conducted, 58 patients with Morbus Hodgkin from December 31, 2018 to December 31, 2023. The inclusion criteria were the newly diagnosed patients. The data were obtained based on the written medical documentation. The statistical analysis was performed by SPSS 22.0, the significance, $p < 0.05$.

Objective: The aims of the study were the analysis of treatment success during the five-year period and the analysis of influence of the clinical stage (CS), extranodal localization, IPS score and bulky disease on the treatment response.

Results: Average age of 58 patients was 40.02 ± 16.01 years. Due to the first-line treatment ABVD, complete remission (CR) was achieved in 67.2%, a partial response 13.8%, whereas disease progression was reported in 19% of the patients. The patients without CR, after six treatment modalities over a five-year period, CR was achieved in 64.5%. Among the 12 mobilized patients, 9 underwent transplantation and achieved CR. The majority of patients (67.3%) was (CS IV and III). The CS and extranodal disease were shown not to correlate with CR ($p > 0.05$). There was a negative correlation between the IPS score and bulky disease with CR, ($p < 0.05$).

Conclusion: The degree of success of first-line treatment for Hodgkin lymphoma is not satisfactory.

Keywords: morbus Hodgkin, ABVD, complete remission (CR)

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POSITRON EMISSION TOMOGRAPHY AFTER TWO CYCLES OF STANDARD CHEMOTHERAPY IN PATIENTS WITH HODGKIN LYMPHOMA

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SAŽETAK

Uvod: Pozitron emisiona tomografija nakon dva ciklusa hemioterapije procenjuje rani terapijski odgovor kod lečenja Hoćkinovog limfoma čime se identifikuju bolesnici sa negativnim odnosno pozitivnim nalazom što predstavlja značajan prognostički faktor. Deeskalacije terapije kod bolesnika sa negativnim nalazom, odnosno povećanje intenziteta terapije kod bolesnika sa pozitivnim nalazom vodi ka redukciji toksičnosti lečenja i poboljšanju ishoda lečenja ovih.

Cilj: Ispitati prognostički značaj nalaza PET/CT2 na ukupno preživljavanje i vreme do progresije bolesti.

Metode: Istraživanje je sprovedeno na Institutu za onkologiju Vojvodine kao retrospektivno-prospektivna studija. Uključeno je 157 bolesnika, sa dijagnostikovanim klasičnim Hoćkinovim limfomom. Svi bolesnici lečeni su hemioterapijom po protokolu ABVD. Kod 66 bolesnika rađena je pozitron emisiona tomografija 2 (PET/CT2) u cilju procene ranog terapijskog odgovora. Populacija bolesnika kod kojih je rađen PET/CT2 podeljena je na dve grupe: bolesnici sa negativnim nalazom PET/CT2 i bolesnici sa pozitivnim nalazom PET/CT2. Statistička analiza izvršena je u programu Medcalc.

Rezultati: Negativan nalaz imalo je 52 (78,7%) bolesnika, 14 (21,3%) bolesnika imalo je pozitivan PET/CT2. Bolesnici sa negativnim PET/CT2 imali su značajno duže vreme do progresije bolesti (PFS) (negativan nalaz PET/CT2, 3-god 88%, medijana nije postignuta; pozitivan nalaz PET/CT2, 3-god 36%, medijana 3 meseca, $p < 0,0001$). Bolesnici sa negativnim nalazom PET/CT2 imali su značajno duže i ukupno preživljavanje (negativan nalaz PET/CT2, 3-god 100%, medijana nije postignuta; pozitivan nalaz PET/CT2, 3-god 73%, medijana nije postignuta, $p = 0,0004$). U multivarijantnoj analizi ukupnog preživljavanja nalaz PET/CT2 je takođe imao značajan uticaj.

Zaključak: Nalaz PET/CT2 nakon drugog ciklusa standardne hemioterapije kod obolelih od Hoćkinovog limfoma predstavlja značajan prognostički faktor.

Ključne reči: Hoćkinova bolest, pozitron emisiona tomografija / kompjuterizovana tomografija, ishod lečenja, analiza preživljavanja

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ABSTRACT

Introduction: Positron emission tomography after two cycles of chemotherapy (PET/CT2) evaluates early therapeutic response in the treatment of Hodgkin lymphoma. In this way, patients with a negative or positive result are identified. Deescalation of treatment in patients with a negative result, and escalation of therapy in patients with a positive result aims to reduce toxicities and improve the outcome of the treatment.

Objective: To evaluate the prognostic significance of PET/CT2 results on overall survival and time to disease progression in patients with Hodgkin lymphoma.

Methods: We conducted a retrospective-prospective study at the Oncology Institute of Vojvodina and included 157 patients diagnosed with classic Hodgkin lymphoma. All patients were treated with ABVD protocol. Positron emission tomography 2 (PET/CT2) was performed in 66 patients. The population of patients who underwent PET/CT2 was divided into two groups: the first group consisted of patients with a negative PET/CT2 result, the second group consisted of patients with a positive PET/CT2.

Results: Negative result was identified in 52 (78.7%) patients, 14 (21.3%) patients had a positive PET/CT2. Patients with a negative PET/CT2 had a significantly longer progression free survival (PFS) (negative PET/CT2, 3-year 88%, median not reached; positive PET/CT2, 3-year 36%, median 3 months, $p < 0.0001$).

Patients with a negative PET/CT2 had significantly longer overall survival (negative PET/CT2 finding, 3-year 100%, median not reached; positive PET/CT2, 3-year 73%, median not reached, $p = 0.0004$). In the multivariate analysis, PET/CT2 also had a significant impact on overall survival.

Conclusion: The result of PET/CT2 in patients with Hodgkin lymphoma is a significant prognostic factor.

Keywords: Hodgkin disease, positron emission tomography / computed tomography, treatment outcome, survival analysis

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PROGNOSTIČKI FAKTORI UKUPNOG PREŽIVLJAVANJA I VREMENA DO PROGRESIJE BOLESTI KOD BOLESNIKA OBOLELIH OD HOČKINOVOG LIMFOMA

PROGNOSTIC FACTORS FOR OVERALL SURVIVAL AND PROGRESSION FREE SURVIVAL IN PATIENTS WITH HODGKIN LYMPHOMA

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SAŽETAK

Uvod: Hoćkinov limfom čini 10% svih limfoma, a leči se primenom hemioterapije ili kombinacijom hemioterapije i zračne terapije u zavisnosti od stadijuma bolesti. Na ovaj način 20% bolesnika ne odgovori na terapiju ili ima relaps bolesti nakon inicijalnog odgovora na terapiju. Stadijum bolesti, godine starosti, prisustvo ekstranodalne bolesti, balki bolest, bolest u kostima, B simptomi i određeni laboratorijski nalazi predstavljaju prognostičke faktore vremena do progresije bolesti i ukupnog preživljavanja bolesnika.

Cilj: Ispitivali smo prognostički značaj starosti bolesnika, pola, stadijuma bolesti, broja leukocita, broja trombocita, nivoa hemoglobina, prisustvo bolesti u kostima bolesnika obolelih od Hoćkinovog limfoma i lečenih na Institutu za onkologiju Vojvodine od 2009–2019. godine.

Metode: Sproveli smo retrospektivno-prospektivno istraživanje u koje je uključeno je 157 bolesnika, sa dijagnostikovanom klasičnim Hoćkinovim limfomom. Statistička analiza izvršena je u programu Medcalc.

Rezultati: Bolesnici u prvom i drugom stadijumu bolesti imali su duže vreme do progresije bolesti (PFS) (3-god 84 % vs. 59 %, medijana nije postignuta (NR) vs. 131 meseci; HR 0,47; $p = 0,006$). Bolest u kostima prilikom inicijalnog određivanja stadijuma bolesti dovodi do kraćeg PFS (ne 3-god 69%, medijana NR; da 3-god 51%, medijana 87 meseci; $p = 0,02$). Broj trombocita veći od 400×10^9 pri započinjanju lečenja dovodi do kraćeg ukupnog preživljavanja ($< 400 \times 10^9$ 3-god 94%, medijana NR; $> 400 \times 10^9$ 3-god 87%, medijana NR; HR 0,28, $p = 0,017$).

Zaključak: Stadijum bolesti, bolest u kostima i broj trombocita utiču značajno na prognozu dok ostali ispitivani faktori nisu značajno uticali na vreme do progresije bolesti niti na ukupno preživljavanje. U multivarijantnoj analizi ukupnog preživljavanja ispitivani parametri nisu imali značajni uticaj.

Ključne reči: Hoćkinova bolest, limfom, prognoza, preživljavanje bez progresije, ukupno preživljavanje

ABSTRACT

Introduction: Hodgkin lymphoma accounts for 10% of all lymphomas. Depending on the stage of the disease it is treated with chemotherapy or a combination of chemotherapy and radiation therapy. Twenty percent of patients do not respond to therapy or have a relapse of the disease after the initial response. Disease stage, age, presence of extranodal disease, bulky disease, B symptoms and certain laboratory findings are prognostic factors of time to disease progression and overall survival of patients with Hodgkin lymphoma.

Objective: To investigate the prognostic significance of the patient's age, sex, stage of the disease, leukocyte count, platelet count, hemoglobin level, bone disease in patients with Hodgkin lymphoma.

Methods: Study included 157 patients treated for classic Hodgkin lymphoma at the Oncology Institute of Vojvodina from 2009–2019. Statistical analysis was performed in Medcalc program.

Results: Patients in stage I and II of the disease had a longer progression free survival (PFS) (3-year 84% vs. 59%, median not reached vs. 131 months; HR 0.47; $p = 0.006$). Presence of bone disease at initial staging led to a shorter PFS (no 3-year 69%, median NR; yes 3-year 51%, median 87 months; $p = 0.02$). Platelet count greater than 400×10^9 prior to treatment led to a shorter overall survival ($< 400 \times 10^9$ 3-year 94%, median NR; $> 400 \times 10^9$ 3-year 87%, median NR; HR 0.28, $p = 0.017$).

Conclusion: Disease stage, bone disease and platelet count were significant prognostic factors. Other evaluated factors did not significantly affect progression free survival or overall survival. In the multivariate analysis of overall survival, the studied parameters had no significant influence.

Keywords: Hodgkin disease, lymphoma, prognosis, progression-free survival, overall survival

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CARDIOTOXICITY OF RADIOTHERAPY IN HODGKIN LYMPHOMA – CASE REPORT

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SAŽETAK

Uvod: Akutni perikarditis je retka komplikacija radioterapije i razvija se tokom nekoliko dana do nekoliko nedelja nakon zračenja. U većini slučajeva prognoza je dobra i zabeležen je dobar terapijski efekat nesteroidnih antiinflamatornih lekova i kolhicina.

Prikaz slučaja: Predstavljamo 21-godišnjeg pacijenta kome je 2022. godine biopsijom tumorske mase mediastinalnog tumora dijagnostikovani klasični Hočkinov limfom u CS II B M+, EORTC/LISA „intermedijarni stadijum“, GHSC „uznapredovali stadijum“. Lečen je hemoterapijom sa 6 ciklusa prema ABVD (adriablastin, bleomicin, vinblastin, dakarbazin) protokolu vođenu pozitronskom emisijom tomografijom sa kompjuterizovanom tomografijom (FDG-PET/CT), kao i radioterapijom (RT TD 36 Gy) zbog zaostale mase u mediastinumu. Šest nedelja nakon RT pacijent je hospitalizovan u jedinicu intenzivnog lečenja zbog preteće tamponade srca. Perikardiocentezom je dobijen serohemoragični sadržaj (500 ml) u kome maligne ćelije nisu nađene. Magnetnom rezonancom srca (CMR) devet dana nakon perikardiocenteze, osim cirkularnog perikardijalnog izliva od 15 mm ispred desne komore, utvrđena je i smanjena ejakciona frakcija leve i desne komore. Na nivou oba sloja perikarda nađena je akumulacija gadolinijuma. Nije primećeno kasno nakupljanje gadolinijuma u miokardu. Postavljena je dijagnoza postiradijacionog perikarditisa. Pacijent je lečen ibuprofenom i kolhicinom u trajanju od 3 meseca. Na kontrolnoj CMR godinu dana kasnije konstatovana je potpuna regresija prethodno opisanih promena (LK EF 63%, DK EF 56%). Na osnovu FDG-PET/CT, postignuta je potpuna metabolička remisija osnovne bolesti.

Zaključak: CMR, pored ehokardiografije i procene kardiovaskularnog rizika, može pomoći u dijagnostici i praćenju bolesnika nakon kardiotskičnih protokola kao i radioterapije mediastinuma.

Ključne reči: kardiotskičnost, radioterapija, perikarditis, magnetna rezonanca

ABSTRACT

Introduction: Acute pericarditis is a rare complication of radiotherapy and develops within days to weeks after radiation. In most cases, the prognosis is good and a good therapeutic effect of nonsteroidal anti-inflammatory drugs and colchicine has been reported.

Case report: We present a 21-year-old patient who was diagnosed with classical Hodgkin lymphoma in 2022 by biopsy of a mediastinal tumor mass, CS II B M+, EORTC/LISA “intermediate stage”, GHSC “advanced stage”. He was treated with chemotherapy with 6 cycles according to the ABVD regimen guided by positron emission tomography with computerized tomography (FDG-PET/CT), as well as radiotherapy (36 Gy) due to a residual mass in the mediastinum. Six weeks after RT, the patient was hospitalized in the intensive care unit because of threatening cardiac tamponade. Cardiac magnetic resonance (CMR) nine days after pericardiocentesis, in addition to a circular pericardial effusion of 15 mm in front of the right ventricle, a reduced ejection fraction of the left and right ventricle was also determined. Accumulation of gadolinium was found at the level of both layers of the pericardium. A diagnosis of post-radiation pericarditis was made. The patient was treated with ibuprofen and colchicine for 3 months. A full regression of the previously described changes was noted on the follow-up MRI of the heart one year later. Based on FDG-PET/CT, complete metabolic remission of the underlying disease was achieved.

Conclusion: CMR, in addition to echocardiography and cardiovascular risk assessment, can help in the diagnosis and follow-up of patients after cardiotoxic protocols as well as radiotherapy of the mediastinum.

Keywords: cardiotoxicity, radiotherapy, pericarditis, magnetic resonance imaging

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CLINICAL CHARACTERISTICS OF PATIENTS DIAGNOSED WITH MORBUS HODGKIN AND TREATED AT THE UCC KRAGUJEVAC – FIVE-YEAR ANALYSIS

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SAŽETAK

Uvod: Hoćkinov limfom (HL) je retka neoplazma limfnog sistema, jedan je od najčešćih karcinoma u odrasloj mladoj populaciji, sa bimodalnom raspodelom.

Cilj: Cilj rada je bio analiza obolelih po polu, starosti, kliničkom stadijumu, bulky formi bolesti, B simptomima i IPS skor.

Metode: Sprovedena je retrospektivna analiza 58 obolelih od Hoćkinovog limfoma (HL) u periodu od 31.12.2018. do 31.12.2023. godine. Uključujući kriterijum novodijagnostikovani bolesnici, podaci dobijeni iz pisane medicinske dokumentacije. Statistička analiza učinjena SPSS 22.0, značajnost je $p < 0,05$.

Rezultati: Istraživanjem je obuhvaćeno 38 (65,5%) muškaraca i 20 (34,5%) žena, prosečne starosti $40,02 \pm 16,01$ godina. Nije utvrđena bimodalna raspodela, mlađih od 30 godina bilo je 34,5%, a starijih od 55 godina 20,6%. Kliničkom stadijumu (III + IV) vs. (I + II) (67,3% vs. 32,7%). „Bulky” bolest u medijastinumu imalo je 48,5%, B simptome 76% obolelih. IPS skor (visok rizik vs. nizak rizik) bio je 51,7% vs. 48,3%. „Bulky” bolest je prisutnija kod mlađih od 45 godina ($p < 0,05$). Na kraju posmatranog perioda od 5 godina živo je 45 (77,6%), dok je preminulo 13 (22,4%) obolelih.

Zaključak: Oboleli od HL su dominantno mlađi od 45 godina sa „bulky” formom bolesti, visokim kliničkim stadijumom i B simptomatologijom, što ukazuje na kasno javljanje lekaru.

Ključne reči: Hoćkinov limfom (HL), bimodalna raspodela, klinički stadijum (CS), bulky bolest, IPS skor

ABSTRACT

Introduction: Hodgkin lymphoma (HL) is a rare malignancy of the lymphoid system, one of the most common cancers diagnosed in the young adult population, with a bimodal distribution.

Objective: The aim of this study was to analyze the patients based on their gender, age, clinical stage (CS), Bulky disease, B symptoms and IPS score.

Methods: A retrospective analysis was conducted, 58 patients diagnosed with HL for the period from December 31, 2018 to December 31, 2023. The inclusion criteria were the newly diagnosed patients. The data were obtained based on the written medical documentation. The statistical analysis was performed by SPSS 22.0, the significance $p < 0.05$.

Results: The research included 38 men (65.5%) and 20 women (34.5%), average age was 40.02 ± 16.01 years. A bimodal distribution was not established, 34.5% of the patients were younger than 30 years and 20.6% of them were older than 55 years. The CS (III + IV) vs. (I + II) was (67.3% vs. 32.7%). 48.5% of the patients had „Bulky” disease in mediastinum, 76% had B symptoms. The IPS score (high risk vs low risk) was (51.7% vs 48.3%). „Bulky” disease is more present in the younger than 45 years ($p < 0.05$). At the end of the observed five-year period, 45 patients were alive (77.6%), whereas 13 patients died (22.4%).

Conclusion: HL patients are predominantly younger than 45 years with the „bulky” disease, late clinical stage and B symptoms, all of which indicates that it took too long for patients to visit their physicians.

Keywords: Hodgkin lymphoma (HL), bimodal distribution, clinical stage (CS), bulky disease, IPS score

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SIGNIFICANCE OF PET/CT GUIDED APPROACH IN HL THERAPY, EXPERIENCE OF A SINGLE CENTER

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SAŽETAK

Uvod: Hoćkinov limfom (HL) je najčešće dijagnostikovani malignitet kod adolescenata starosti od 15 do 19 godina. Napredak u dijagnostici i lečenju HL je upotreba PET/CT u preciznom stadiranju bolesti i planiranju lečenja.

Cilj: Procena efikasnosti upotrebe PET/CT vođenog pristupa u lečenju novodijagnostikovanih pacijenata sa HL.

Metode: Retrospektivna analiza novodijagnostikovanih HL u IORS-u u periodu od 2016. do 2023. godine, kod kojih je rađen inicijalni, interim i PET/CT na završetku lečenja.

Rezultati: Uključeno je 30 pacijenata sa medijanom starosti 34 (opseg 18–54) godine. Medijana praćenja je bila 47 meseci (opseg 7–91), bez smrtnih ishoda. Najzastupljeniji histološki podtip je bio nodularna skleroza. 18 pacijenata je imalo uznapredovali stadijum bolesti, a 11 pacijenata IV klinički stadijum (CS). Svi pacijenti u CS I i II su imali na interim PET/CT Deauville skor (DS) 1–3, dok je 7 od 17 pacijenata u CS III/IV imalo DS 4–5, $p < 0,05$. Pacijenti u CS I i II su u primali 4 ciklusa hemioterapije, a pacijenti u CS III i IV 6, $p < 0,001$. Kod svih pacijenata je lečenje otpočeto sa ABVD protokolom. Kod 5 pacijenata je, nakon interim PET/CT, promenjena terapija na eBEACOPP protokol, od kojih je tri pacijenta na kraju lečenja imalo DS 1–3, a dva DS 5. Zračenje rezidualne bolesti je imalo 7 pacijenata sa uznapredovalim stadijumom bolesti koji su primali ABVD protokol, $p < 0,05$. Nema razlike u praćenju pacijenta u odnosu na CS nakon završenog lečenja.

Zaključak: PET/CT doprinosi adekvatnom stadiranju pacijenata, posebno u uznapredovalom stadijumu, kao i lečenju u smislu balansiranja između efikasnosti i toksičnosti terapije.

Ključne reči: Hoćkinov limfom, PET, Deauville skor, ABVD, eBEACOPP

ABSTRACT

Introduction: Hodgkin lymphoma (HL) is the most frequently diagnosed malignancy in adolescents aged 15–19 years. Advances in the diagnosis and treatment of HL are the use of PET/CT in precise disease staging and treatment planning.

Objective: Evaluation of the use of PET/CT guided approach in the treatment of newly diagnosed patients with HL.

Methods: Retrospective analysis of HL patients in IORS diagnosed and treated between 2016–2023, in which initial, interim and PET/CT at the end of treatment were performed.

Results: 30 patients with a median age of 34 (range 18–54) years with median follow-up 47 months (range 7–91), with no deaths. 18 patients had advanced stage disease, and 11 had clinical stage (CS) IV. All patients in CS I and II had an interim PET/CT Deauville score (DS) 1–3, while 7 out of 17 patients in CS III/IV had DS 4–5, $p < 0.05$. All patients initially received the ABVD protocol. In 5 patients, after the interim PET/CT, the therapy was changed to the eBEACOPP protocol, of which three patients had DS 1–3 and two DS 5 at the end of the treatment. Radiation therapy was performed in 7 patients with advanced stage disease. There is no difference in the duration of patient follow-up compared to CS after treatment.

Conclusion: PET/CT contributes to the adequate staging of patients, especially in the advanced stage, as well as to treatment in terms of balancing the efficacy and toxicity of therapy.

Keywords: Hodgkin lymphoma, PET, Deauville score, ABVD, eBEACOPP

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MULTIPLI MIJELOM I AL AMILOIDOZA

MULTIPLE MYELOMA AND AL AMYLOIDOSIS

FREQUENCY OF CYTOGENETIC ABNORMALITIES IN NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA – SINGLE CENTER EXPERIENCE

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SAŽETAK

Uvod: Citogenetske abnormalnosti (CA) su prisutne kod velikog broja novodijagnostikovanih bolesnika sa multiplim mijelomom (NDMM). Imaju uticaj na patogenezu, tok i ishod bolesti. Koriste se u stratifikaciji rizika kod NDMM i deo su prognostičkih modela R-ISS, R2-ISS. Detektuju se metodom fluorescentne in situ hibridizacije (FISH).

Cilj: Prikaz učestalosti CA kod NDMM bolesnika lečenih na Klinici za hematologiju Kliničkog centra Vojvodine.

Metode: U retrospektivno istraživanje je uključeno 63 NDMM bolesnika (29 muškaraca i 34 žene). Demografske karakteristike bolesnika, prognostički parametri, CA su analizirani deskriptivnim statističkim metodama u programu Microsoft Office Excel.

Rezultati: Medijana starosti NDMM je bila 63 godine. Kod 50% ispitanika su detektovane CA standardnog rizika, kod 13,46% uočena je CA intermedijarnog rizika, a 36,46% bolesnika je imalo CA visokog rizika. Kod 28,85% bolesnika nije detektovana nijedna CA, a kod 21,15% bolesnika su detektovne 3 i više CA istovremeno. Najčešće udružene mutacije bile su del 13q14 i t(4;14) koje su istovremeno otkrivene kod 17,31% pacijenata. „Double hit“ CA imalo je 15,38% bolesnika. U odnosu na skorove prognostičkih modela, bolesnici su bili 73,47% R-ISS II, 18,37% R-ISS III, 24,49% R2-ISS II, 53,06% R2-ISS III i 12,24% R2-ISS IV.

Zaključak: Epidemiološki prikaz učestalosti CA kod NDMM u našem centru je osnov za buduća istraživanja sa ciljem procene njihovih prognostičkih karakteristika.

Cljučne reči: CA, NDMM, stratifikacija rizika, prognoza

ABSTRACT

Introduction: Cytogenetic abnormalities (CA) are present in a large number of newly diagnosed patients with multiple myeloma (NDMM). They have an influence on the pathogenesis, course and outcome of the disease. They are used in risk stratification and are part of the prognostic scoring systems: R-ISS, R2-ISS. Fluorescent in situ hybridization (FISH) is a method for detecting CA.

Objective: Presentation of the frequency of CA in NDMM patients treated at the Clinic for hematology at the Clinical Center of Vojvodina.

Methods: This retrospective study included 63 NDMM patients (29 men and 34 women). Demographic characteristics of patients, prognostic parameters and CA were analyzed by descriptive statistical methods in the Microsoft Office Excel program.

Results: The median age of NDMM patients was 63 years. Standard risk CA were detected in 50% of patients, 13.46% had intermediate risk CA and 36.46% of the patients had high risk CA. In 28.85% of patients no CA were detected, and in 21.15% of patients 3 or more CA were detected simultaneously. The most common associated mutations were del 13q14 and t(4;14), which were simultaneously detected in 17.31% of patients. „Double hit“ CA were present in 15.38% of patients. According to the prognostic scoring systems, 73.47% of patients were R-ISS II, 18.37% R-ISS III, 24.49% R2-ISS II, 53.06% R2-ISS III and 12.24% were R2-ISS IV.

Conclusion: Epidemiological study of the frequency of CA in NDMM in our center is the basis for future research of their prognostic characteristics.

Keywords: CA, NDMM, risk stratification, prognosis

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PRESENTATION AND OUTCOMES OF PATIENTS WITH MULTIPLE MYELOMA TREATED OVER FIVE YEARS AT THE UŽICE GENERAL HOSPITAL

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SAŽETAK

Uvod: Ishodi pacijenata sa multiplim mijelomom su značajno poboljšani uvođenjem novih agenasa.

Cilj: Analiza rezultata lečenja pacijenata sa multiplim mijelomom lečenih od januara 2019. do maja 2024.

Metode: Obuhvaćeno je 53 bolesnika (m/ž:30/23 = 1,3:1) prosečne starosti 64 godine (40–77).

Rezultati: Distribucija u odnosu na tip, klinički stadijum (CS), prognostički index (ISS) odgovarala je standardnoj populaciji: 1. Tip mijeloma IgG/A/BJ = 35/7/10. 2. Klinički stadijum: CS3/2/1 = 44/2/3. 3. ISS2,3/RISS2,3 = 39/42. 4. FISH nepovoljan/uređan/nije rađen = 16/27/8. Anemiju je imalo 17, bubrežnu insuficijenciju 17, osteolizu 24, visok LDH 8, patološku frakturu 12, ekstramedularnu bolest 8, amiloidozu 3. U prvoj liniji bortezomib je dat kod 93,3% kroz protokole: CVD/VTD/MPV/CTD/HDexa = 25/15/1/8/1. Autologa transplantacija matičnim ćelijama (aTMČH) je sprovedena kod 12/53. Povoljan odgovor je imalo 42/53, stabilnu bolest 2/53, progresiju 3/53, smrtni ishod 2/53. Medijana vremena do progresije je iznosila 13 meseci. U prvom relapsu je lečeno 12/53 različitim protokolima a najčesće je primenjen daratumumab 7/12. Povoljan odgovor je imalo 10/12, a 2 su preminula. Medijana ukupnog preživljavanja za period praćenja je 22 meseca (0–64), a kod lečenih daratumumabom nije dostignuta. Dvogodišnje ukupno preživljavanje je imalo > 75% bolesnika, a preživljavanje bez progresije > 65%. Tokom perioda praćenja remisija se održava kod 31/53 (58%) dok je ukupno preminulo 9/53 (17%) pacijenata. Svi preminuli su imali nepovoljan prognostički skor, 8/9 3CS, 6/9 >70 godina, samo 1 aTMČH, kardiološke komorbiditete 5/9 a 7/9 neki od: dijabetes, hipotireoza, HTA, BHP.

Zaključak: Primena novih modaliteta kao što su monoklonska antitela značajno utiče na preživljavanje i kvalitet života.

Ključne reči: multipli mijelom, inhibitor proteozoma, imunomodulator

ABSTRACT

Introduction: Outcomes for patients with multiple myeloma have significantly improved with new agents.

Objective: Analysis of treatment outcomes for multiple myeloma patients treated from January 2019 to May 2024.

Methods: The study included 53 patients (30 men, 23 women; ratio 1.3:1) with an average age of 64 years (range 40–77).

Results: Patient distribution by myeloma type, clinical stage (CS), and prognostic index (ISS) was consistent with standard populations: 1) Myeloma type: IgG 35, IgA 7, BJ 10. 2) Clinical stage: CS3 44, CS2 2, CS1 3. 3) ISS 2,3/RISS 2,3: 39/42. 4) FISH results: unfavorable 16, normal 27, not done 8. Clinical issues included anemia (17), renal insufficiency (17), osteolysis (24), high LDH (8), pathological fractures (12), extramedullary disease (8), amyloidosis (3). Most patients received new agents like proteasome inhibitors or immunomodulators. In first-line treatment, bortezomib was used in 93.3% of patients through protocols: CVD/VTD/MPV/CTD/HDexa (25/15/1/8/1). Autologous stem cell transplantation (aSCT) got 12 patients. Favorable response had 42, stable disease 2, progression 3, and 2 died. The median time to progression was 13 months. At first relapse, 12 received protocols including daratumumab, achieving a favorable response in 10 cases and 2 deaths. The median overall survival was 22 months (range 0–64), with a two-year overall survival rate > 75% and progression-free survival > 65%. Remission was maintained in 31/53 patients (58%), with 9/53 (17%) deaths.

Conclusion: Treatment results are comparable to other centers, showing survival benefits from new modalities like monoclonal antibodies.

Keywords: multiple myeloma, proteasome inhibitor, immunomodulator

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EXPIRIENCE OF UŽICE GENERAL HOSPITAL IN TREATING RELAPSED/REFRACTORY MULTIPLE MYELOMA (MM) WITH DARATUMUMAB

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SAŽETAK

Uvod: Daratumumab utiče na preživljavanje u RRMM.

Cilj: Rezultati lečenja daratumumabom u RRMM.

Metode: Retrospektivna analiza primene daratumumaba kod 7 pacijenata u periodu od 14. marta 2022. do 14. maja 2024. u OB Užice

Rezultati: Lečena su 4 muškarca i 3 žene, srednje starosti od 65 godina, koji su bili u III kliničkom stadijumu, 2 sa EM bolešću. Najčešći je bio MM IgG tip. Daratumumab je kombinovan sa deksazonom i bortezomibom kod 2, lenalidomidom kod 4 i kod 1 pacijenta kao monoterapija. Kao treća linija lečenja kod 4 pacijenta, druga kod 2 a kao četvrta kod 1. Nepovoljan FISH je imalo troje. Prema broju primenjenih ciklusa podeljeni su u grupe (do 2 i više od 2 ciklusa). Pet je dobilo intravenski, dva subkutani oblik leka. Preminula su dva pacijenta pre kraja 2. ciklusa. Pet pacijenata je imalo biohemijsku i kliničku remisiju posle 2 ciklusa. Kod jednog pacijenta je lečenje prekinuto zbog kardioloških komplikacija. Preživljavanje bez progresije bolesti je zabeleženo kod 5 pacijenata u grupi koja je primila više od 2 ciklusa, uključujući i one sa nepovoljnim aberacijama, uz očuvan ECOG PS 0–1. Medijana preživljavanja nije dostignuta.

Zaključak: Primena daratumumaba utiče na dužinu ukupnog preživljavanja i dužinu preživljavanja bez progresije uz očuvan kvalitet života. Primena leka u kasnijim linijama lečenja i prisustvo EM bolesti negativno utiču na preživljavanje.

Ključne reči: multipli mijelom, relaps, daratumumab, preživljavanje

ABSTRACT

Introduction: Daratumumab impacts the survival of patients with RRMM.

Objective: Presenting treatment outcomes with daratumumab in RRMM.

Methods: Retrospective analysis of the administration of daratumumab for 7 patients from 14. March 2022 – 14. May 2024 at Užice General Hospital.

Results: Four male, and three female patients were treated with the median age being 65, all were in stage 3 of the clinical trial, with two having extramedullary disease. The most common was IgG myeloma. daratumumab was administered with dexamethasone and bortezomib in 2, lenalidomide in 4, and as monotherapy in 1 patient. It was applied as the third line therapy in 4, as the second line therapy in 2, and as the fourth line therapy in 1 patient. Three patients had unfavorable FISH results.

Patients were divided in 2 groups: 2 and more than 2 cycles. Five patients received daratumumab intravenously, and two subcutaneously. Two patients died before the 2nd cycle was finished. Progression-free survival was recorded in all 5 patients in the group that received more than 2 cycles, including those with unfavorable aberrations, with preserved ECOG PS 0–1. The median survival rate was not reached.

Conclusion: The application of daratumumab significantly affects overall survival and progression-free survival with preserved life quality. Administration of daratumumab in later lines of treatment and the presence of extramedullary disease negatively affect survival.

Keywords: multiple myeloma, relapse, daratumumab, survival

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PROGNOSTIČKI ZNAČAJ HEMATOLOŠKIH PARAMETARA KOD NOVODIJAGNOSTIKOVANIH BOLESNIKA SA MULTIPLIM MIJELOMOM (NDMM)

PROGNOSTIC SIGNIFICANCE OF HEMATOLOGICAL PARAMETERS IN NEWLY DIAGNOSED PATIENTS WITH MULTIPLE MYELOMA (NDMM)

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SAŽETAK

Uvod: Imajući u vidu već poznate interakcije između tumorskog mikrookruženja i imunološkog sistema obolelog od multiplog mijeloma, evidentan je i mogući uticaj hematoloških parametara (HP) – apsolutnog broja neutrofilnih granulocita (ABN), apsolutnog broja limfocita (ABLy) i apsolutnog broja monocita (ABM) na tok bolesti i ishod lečenja.

Cilj: Ispitati kod NDMM prediktivni značaj: ABN, ABLy, ABM, kao i odnosa ABN/ABLy („neutrophil lymphocyte ratio“, NLR) i odnosa ABM/ABLy („monocyte lymphocyte ratio“, MLR).

Metode: Istraživanje je sprovedeno kao retrospektivna analiza lokalne baze podataka našeg centra i obuhvatilo je 233 NDMM u periodu od 2018. do 2023. godine. Demografske karakteristike bolesnika, prognostički parametri, HP, NLR, MLR su analizirani deskriptivnim statističkim metodama. Analize korelacije HP, NLR i MLR sa ISS grupama rizika obolelih su sprovedene u SPSS programu, v.22.

Rezultati: U ispitivanoj grupi je bilo 128 muškaraca (54,94%), prosečne starosti 67 godina, u rasponu 31–86 godina i 105 žena (45,06%), prosečne starosti 66 godina, u rasponu 25–92 godine. U odnosu na grupe rizika, bilo je 17,14% u ISS1, 31,84% ISS2 i 50,75% bolesnika u ISS3. Statistički duže preživljavanje je detektovano kod ISS1 bolesnika u odnosu na ISS3 ($p = 0,000$) kao i kod ISS2 u odnosu na ISS3 grupu bolesnika ($p = 0,003$). Detektovan je statistički značajno manji ABM u grupi ISS1 u odnosu na ISS2 ($p = 0,025$), kao i u grupi ISS1 u odnosu na ISS3 ($p = 0,027$). Detektovana je statistički značajno manja vrednost MLR u grupi ISS1 u odnosu na ISS3.

Zaključak: Veće vrednosti ABM i MLR se mogu smatrati pokazateljima lošije prognoze kod NDMM.

Ključne reči: ABN, ABLy, ABM, NLR, MLR, NDMM

ABSTRACT

Introduction: As interactions between tumor microenvironment and immune system in NDMM are already known, the possible influence of hematological parameters (HP) – the absolute count of neutrophils (ACN), the absolute count of lymphocytes (ACLy) and the absolute count of monocytes (ACM) on the course of the disease and the treatment response is evident.

Objective: Analysis of predictive significance of: ACN, ACLy, ACM, ACN/ACLy („neutrophil lymphocyte ratio“, NLR) and ACM/ACLy („monocyte lymphocyte ratio“, MLR).

Methods: This research was conducted as a retrospective analysis of the local database of our center and included 233 NDMM patients treated from 2018 to 2023. Demographic characteristics of patients, prognostic parameters, HP, NLR, MLR were analyzed by descriptive statistical methods. Statistical analysis of correlations was performed using the SPSS program, v.22.

Results: There were 128 men (54.94%), average age of 67, in the range of 31–86 years and 105 women (45.06%), average age of 66, in the range of 25–92 years. There were 17.14% patients in ISS1, 31.84% in ISS2 and 50.75% patients in ISS3 group of risk. Longer survival was detected in ISS1 compared to ISS3 ($p = 0.000$) as well as in ISS2 compared to ISS3 ($p = 0.003$). Lower values of ACM were detected in the ISS1 compared to ISS2 ($p = 0.025$), as well as in the ISS1 compared to ISS3 ($p = 0.027$). Lower MLR values were detected in the ISS1 compared to ISS3 ($p = 0.018$).

Conclusion: Higher values of ABM and MLR can be considered as predictors of worse prognosis in NDMM.

Keywords: ABN, ABLy, ABM, NLR, MLR, NDMM

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CAUSES OF EARLY MORTALITY IN ELDERLY PATIENTS DURING MULTIPLE MYELOMA TREATMENT – DATA FROM CLINICAL PRACTICE

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SAŽETAK

Uvod: Multipli mijelom je maligna bolest dobro diferentovanih, zrelih, obično sporo proliferišućih B limfocita tj plazmocita. Godišnja incidenca oboljenja iznosi 3–4 bolesnika na 100 000. Srednja starost pri postavljanju dijagnoze je 69 godina; a oko 10% je starije od 85 godina. Sa razvojem novih terapijskih modaliteta poslednjih decenija, preživljavanje obolelih pacijenata se značajno poboljšalo. Međutim, ishodi lečenja za gerijatrijsku populaciju pacijenata sa MM su često nezadovoljavajući, uslovljeni komorbiditetima i povećanim ispoljavanjem neželjenih efekata terapije.

Cilj: Prikaz rezultata iz stvarne kliničke prakse koji se odnose na rani mortalitet starijih pacijenata lečenih od multiplog mijeloma u Vojnomedicinskoj akademiji, kao i neposredni uzroci ranog mortaliteta.

Metode: Prikazani su rezultati retrospektivne analize pacijenata lečenih od MM u Klinici za hematologiju VMA u periodu od 2007. do 2022. godine. Različite kliničke karakteristike pacijenata i laboratorijski parametri pri postavljanju dijagnoze su analizirani da se utvrdi njihov uticaj na rani mortalitet.

Rezultati: Univarijantna analiza je izdvojila starost pacijenata ≥ 75 godina prilikom postavljanja dijagnoze multiplog mijeloma kao prediktor ranog mortaliteta (OR 0,174, 95% CI 0,039–0,773, $p = 0,022$). Ostali klinički i laboratorijski parametri od interesa nisu pokazali statističku značajnost.

Zaključak: U našoj analizi, od 41 pacijenta rani mortalitet se ispoljio kod 14 (34,1%), i jedino se starost pacijenta ≥ 75 godina izdvojila kao nezavisan prediktor ranog mortaliteta. Najčešći uzrok rane smrtnosti je bila infekcija (50%).

Ključne reči: multipli mijelom, rani mortalitet, klinička praksa

ABSTRACT

Introduction: Multiple myeloma is a malignant disease of well-differentiated, mature, slowly proliferating B lymphocytes, i.e. plasma cells. The annual incidence of the disease is 3–4 per 100,000 patients. Most frequently, it affects the elderly; median age at diagnosis is 69, and around 10% are older than 85. As new therapeutic modalities developed in recent decades, survival of affected patients significantly improved. However, outcome of the treatment of the geriatric population of patients with MM is often unsatisfactory due to comorbidities and increased side effects of the therapy.

Objective: Presentation of results of the actual clinical practice concerning early mortality in elderly patients treated for MM at the Military Medical Academy, including its immediate causes.

Methods: Presentation of results of a retrospective analysis of patients treated for MM at the Hematology Clinic, MMA, between 2007 and 2022. The analysis covered various clinical characteristics of patients and laboratory parameters during diagnostic procedures in order to determine their impact on early mortality.

Results: Univariate analysis has singled out the patients' age of 75+ when diagnosed with multiple myeloma as predictive of early mortality (OR 0.174, 95% CI 0.039–0.773, $p = 0.022$).

Other clinical and laboratory parameters of interest were statistically non-significant.

Conclusion: Our analysis has shown that 14 out of 41 patients were affected by early mortality (34.1%), and it was only the patients' age – 75 years and above – that stood out as an independent predictor of early mortality. The most common cause of early mortality was infection (50%).

Keywords: multiple myeloma, early mortality, clinical practice

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MULTIPARAMETER FLOW CYTOMETRY IN THE DETECTION OF CIRCULATING MYELOMA PLASMA CELLS AT THE DIAGNOSIS

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SAŽETAK

Uvod: Visoki nivoi cirkulišućih mijelomskih plazma ćelija (CMPČ) kod bolesnika na dijagnozi predstavljaju marker agresivne bolesti.

Cilj: Optimizacija metodologije multiparametarske protočne citometrije za visoko senzitivnu detekciju CMPČ.

Metode: Ispitivanje je sprovedeno u grupi od 34 bolesnika sa de novo multiplim mijelomom, pre primene terapije. Uzorci periferne krvi su obeležavani primenom dve 8-kolorne-kombinacije monoklonskih antitela. Analiza uzoraka je urađena na protočnom citometru BD-FACSCantoll/BD-FACSDiva softver. CMPČ su izražavane u relativnim (% CD45+ ćelija) odnosno apsolutnim vrednostima (ćelije/μl) primenom metodologije dvostruke-platforme. U cilju pouzdane detekcije i kvantifikacije, prikupljano je najmanje 50 CMPČ / 2x10⁶ CD45+ ćelija.

Rezultati: Analiza CMPČ pokazala je prisustvo imunofenotipskih aberacija u ekspresiji leukocitnih molekula sa sledećom učestalošću: CD19neg (100%), CD81neg (87%), CD45+low (95%), CD56+ (85%), CD117+ (40%). Monoklonalna ekspresija cytlgk (85%) predominirala je u poređenju sa ekspresijom cytlgl (15%) lanca. CMPČ su detektovane sa učestalošću od 59% (20/34 bolesnika). Tom prilikom su u proseku bile prikupljene 4472 CMPČ (opseg, 46–58879 ćelija) od prosečno analiziranih 2,8x10⁶ CD45+ ćelija (opseg, 1–4,4x10⁶ ćelija). Prosečna vrednost detektovanih CMPČ je iznosila 0,211% CD45+ ćelija (opseg, 0,001–3,114 %) odnosno 8,8 ćelija/μl (opseg, 0,14–112,1 ćelija/μl). Deo bolesnika u našoj grupi je imao vrednost CMPČ ≥ 5 ćelija/μl (6/20, 30%).

Zaključak: U našoj grupi bolesnika utvrđen je specifičan aberantan imunofenotipski profil CMPČ (CD38+CD138+CD19negCD81negCD56+CD117neg/+CD45+low/SSCmedium), na osnovu koga je ova populacija detektovana sa učestalošću od 59% (senzitivnost detekcije 2x10⁻⁵). Nivo CMPČ, povezan sa agresivnom bolešću, ispoljilo je 30% bolesnika na dijagnozi.

Ključne reči: multipli mijelom, cirkulišuće plazma ćelije, imunofenotip, protočna citometrija

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ABSTRACT

Introduction: High levels of circulating myeloma plasma cells (CMPC) in patients undergoing diagnosis are a marker of aggressive disease.

Objective: Optimizing the methodology of multiparameter flow cytometry for highly sensitive detection of CMPC.

Methods: The study included 34 patients with de novo multiple myeloma. Peripheral blood samples were labeled using two 8-color-combinations of monoclonal antibodies. Analysis was performed on a flow cytometer BD-FACSCantoll/BD-FACSDiva software. CMPC were expressed in relative (% CD45+ cells) and absolute values (cells/μl) using the dual-platform methodology. For reliable quantification, at least 50 CMPC / 2x10⁶ CD45+ cells were collected.

Results: CMPC analysis showed the presence of immunophenotypic aberrations in the expression of leukocyte molecules with the following frequency: CD19neg (100%), CD81neg (87%), CD45+low (95%), CD56+ (85%), CD117+ (40%). Monoclonal cytlgk (85%) expression predominated compared to cytlgl (15%). CMPC were detected with a frequency of 59% (20/34 patients). On that occasion, an average of 4472 CMPC (range, 46–58879 cells) were collected from an average of 2.8x10⁶ CD45+ cells analyzed (range, 1–4.4x10⁶ cells). The average value of detected CMPC was 0.211% CD45+ cells (range, 0.001–3.114 %) or 8.8 cells/μl (range, 0.14–112.1 cells/μl). Part of the patients in our group had a CMPC value ≥ 5 cells/μl (6/20, 30%).

Conclusion: In our group, a specific aberrant immunophenotypic profile of CMPC was determined (CD38+CD138+CD19negCD81negCD56+CD117neg/+CD45+low/SSCmedium), based on what this population was detected with a frequency of 59% (sensitivity of detection 2x10⁻⁵). The level of CMPC, associated with an aggressive disease, was manifested by 30% of patients at diagnosis.

Keywords: multiple myeloma, circulating plasma cells, immunophenotype, flow cytometry

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EXTRAMEDULLARY DISEASE IN MULTIPLE MYELOMA: CLINICOBIOLOGICAL CHARACTERISTICS AND PROGNOSTIC IMPACT

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SAŽETAK

Uvod: Nalaz ekstrapredularne bolesti (EMD) pri dijagnozi multiplog mijeloma (NDMM) karakteriše agresivni oblik bolesti.

Cilj rada je bio analiza kliničko-bioloških karakteristika NDMM pacijenata sa EMD i njen prognostički uticaj.

Metode: Istraživanje je obuhvatilo 88 NDMM pacijenata dijagnostikovanih u periodu 2001–2023, sa EMD lokalizacijom: paraskeltni kod 61 pacijenta (69,3%) i ekstraoselni plazmocitom (EOP) kod 27 pacijenata (30,7%). Lokalizacije EOP: gastrointestinalni trakt kod 7 pacijenata, respiratorni trakt kod 6, pljuvačna žlezda kod 6, limfni čvor kod 3, štitasta žlezda kod 1 pacijenta, slezina kod 3 i testisi kod 1 pacijenta. U skladu sa revidiranim ISS skorom, R-ISS1 je imalo 28 pacijenata (31,8%), R-ISS2 46 (52,2%), a R-ISS3 14 (15,9%) pacijenata. Kod 32 od 74 pacijenta sa FISH nalazima (43,2%) otkrivene su sledeće hromozomske abnormalnosti visokog rizika (CA): del17p kod 8 (10,8%), amp1q kod 16 (21,6%), t(4;14) kod 4 (5,4%) i t(14;16) kod 4 (5,4%) pacijenta. Bortezomibom je lečeno 48 pacijenata (45,5%). Autologa transplantacija matičnih ćelija hematopoeze (ASCT) sprovedena je kod 26 bolesnika (29,5%).

Rezultati: Povoljan terapijski odgovor (ORR $\geq$ PR) postignut je kod 76 pacijenata (86,4%). Paraskeltna EMD se karakterisala dužim PFS u poređenju sa EOP, bez statističke značajnosti ($p = 0,526$). Uprkos dužem OS pacijenata sa paraskeltnim EMD, nije bilo statističke razlike u odnosu na pacijente sa EOP ($p = 0,995$). OS pacijenata sa visokorizičnim CA i paraskeltnim EMD bio je duži u poređenju sa pacijentima sa visokorizičnim EOP mijelomom, ali bez statističke značajnosti ($p = 0,684$).

Zaključak: Pacijenti sa EOP mijelomom se odlikuju visokorizičnim karakteristikama, ukazujući na potrebu za intenzivnijim lečenjem sa novim terapijskim modalitetima.

Ključne reči: multipli mijelom, ekstrapredularna bolest, kliničko-biološke karakteristike

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ABSTRACT

Introduction: Extramedullary disease (EMD) in newly diagnosed multiple myeloma (NDMM) patients is generally considered as aggressive form of disease.

Objective was to analyze clinicobiological characteristics of NDMM patients with EMD and its prognostic impact.

Methods: The study included 88 NDMM patients diagnosed during period 2001–2023, with EMD localization: paraskeltnal in 61 patients (69.3%) and extraosseal plasmocytoma (EOP) in 27 patients (30.7%). The localizations of the EOP were as follows: gastrointestinal tract 7 patients, respiratory system 6, salivary gland 6, lymph nodes 3, thyroid gland 1, spleen 3, and testicles 1 patient. Regarding Revised-ISS score, R-ISS1 had 28 patients (31.8%), R-ISS2 46 (52.2%) and R-ISS3 had 14 (15.9%). In 32 of 74 patients with FISH findings (43.2%), following high-risk chromosomal abnormalities (CAs) were detected: del17p in 8 (10.8%), amp1q in 16 (21.6%), t(4;14) in 4 (5.4%), and t(14;16) in 4 (5.4%). Bortezomib based chemotherapy was applied in 48 patients (45.5%). Autologous stem cell transplantation (ASCT) was performed in 26 patients (29.5%).

Results: Overall response rate (ORR $\geq$ PR) was achieved in 76 patients (86.4%). Patients with paraskeltnal EMD had longer PFS in comparison to the patients with EOP, although without statistical significance ($p = 0.526$). Regarding OS, despite longer OS of the patients with paraskeltnal EMD, there was no statistical difference in comparison to the patients with EOP ($p = 0.995$). The OS of patients with high-risk CAs associated with paraskeltnal EMD was longer in comparison to patients with CAs high-risk EOP myeloma but without statistical significance ($p = 0.684$).

Conclusion: Patients with EOP myeloma are characterized with high-risk features and that indicates more intensive treatment with new treatment modalities.

Keywords: multiple myeloma, extramedullary disease, clinicobiological characteristics

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THE SIGNIFICANCE OF VITAMIN B12 DEFICIENCY IN PATIENTS WITH MULTIPLE MYELOMA: A SINGLE-CENTER PILOT STUDY

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SAŽETAK

Uvod: Multipli mijelom (MM) je neizlečivo oboljenje koje značajno utiče na kvalitet života bolesnika. Deficit vitamina B12 prepoznat je kao nepovoljan prognostički faktor kod solidnih maligniteta, ali nije opsežnije ispitivan kod bolesnika sa MM.

Cilj: Procena povezanosti deficita koncentracije serumskog vitamina B12 sa laboratorijskim, kliničkim parametrima i terapijskim odgovorom kod bolesnika sa novodijagnostikovanim MM.

Metode: Retrospektivnom analizom obuhvaćeno je 55 uzastopnih bolesnika sa MM dijagnostikovanih i lečenih u Službi hematologije KBC „Zemun“ između 2021. i 2023. godine. Prema nivoima vitamina B12, bolesnici su podeljeni u grupu A (< 150 pmol/L, 26% bolesnika) i grupu B (≥ 150 pmol/L, 74% bolesnika).

Rezultati: Grupe A i B se nisu značajno razlikovale u odnosu na starosno doba, pol, funkcionalni status, prisustvo trombotskog događaja pri dijagnozi, kao ni u relevantnim laboratorijskim parametrima, uključujući nivoe hemoglobina, laktat-dehidrogenaze, serumskog albumina, kalcijuma, kreatinina i beta2-mikroglobulina. Većina bolesnika iz obe grupe imala je IgG tip MM, infiltraciju koštane srži preko 60% i visokorizičnu bolest na prezentaciji (A:ISS III-50%, R-ISS III-43,8%, R2-ISS visok – 42,9%; B:ISS III-47%, R-ISS III-42%, R2-ISS visok – 39%, $p > 0.05$). Sa druge strane, periferna polineuropatija na prezentaciji je bila značajno češća u grupi A (A:56,8% vs. B:16,7%, $p = 0.02$). Koncentracija Vitamina B12 nije uticala na stopu dobrog odgovora na prvu terapijsku liniju (postizanje barem veoma dobre parcijalne remisije) – A:40% vs. B: 43%, $p = 0.37$.

Zaključak: Deficit vitamina B12 je čest kod simptomatskog MM i može doprineti perifernoj polineuropatiji, što smanjuje kvalitet života i ograničava optimalne terapijske pristupe. Rezultati naše pilot studije zavređuju dalja istraživanja.

Ključne reči: multipli mijelom, deficit vitamina B12, periferna polineuropatija, terapijski odgovor

ABSTRACT

Introduction: Multiple myeloma (MM) remains an incurable disease that significantly impacts patients' quality of life. Vitamin B12 deficiency is proven to be a significant adverse prognostic factor in solid neoplasms, but has not been comprehensively evaluated in MM.

Objective: To evaluate the correlation of low serum vitamin B12 concentrations of newly diagnosed MM patients with laboratory and clinical parameters, end-organ damage, and treatment response.

Methods: Medical records of 55 consecutive MM patients diagnosed at the Department of Hematology, UCHC "Zemun" between 2021-2023 were retrospectively analyzed. According to B12 levels, patients were divided into Group A (< 150 pmol/L, 26% of patients) and Group B (≥ 150 pmol/L, 74% of patients).

Results: Groups A and B showed no significant differences in age, sex, functional state and presence of thrombotic events at diagnosis, as well as disease-related laboratory parameters, including hemoglobin, lactate dehydrogenase, serum albumin, calcium, creatinine, and beta2-microglobulin levels. Both groups predominantly had IgG MM, > 60% plasma cell infiltration of bone marrow, and high-risk disease at presentation (A:ISS III-50%, R-ISS III-43.8%, R2-ISS high – 42.9%; B:ISS III-47%, R-ISS III-42%, R2-ISS high – 39%, $p > 0.05$). However, peripheral neuropathy was significantly more prevalent in group A (A:56.8% vs. B:16.7%, $p = 0.02$). Patients in both groups achieved a comparable rate of at least a very good partial remission with first-line therapy (40% vs. 43%, $p = 0.37$).

Conclusion: B12 deficiency is common in symptomatic MM and may contribute to peripheral neuropathy, which impairs quality of life and limits optimal therapeutic approaches. The results of our pilot study warrant further research.

Keywords: multiple myeloma, vitamin B12 deficiency, peripheral neuropathy, treatment response

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CARDIAC AL AMYLOIDOSIS: THE DIAGNOSTIC CHALLENGES AND PROGNOSTIC IMPACT

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SAŽETAK

Uvod: Kardijalna amiloidoza je prisutna kod 80% novodijagnostikovanih bolesnika sa AL amiloidozom.

Cilj rada je bio ispitati klinički i prognostički značaj nalaza kardijalne zahvaćenosti.

Metode: Istraživanje je obuhvatilo 60 novodijagnostikovanih pacijenata (januar 2015 – jun 2023). Zahvaćenost srca je utvrđena kod 51 pacijenta (85%). Ehokardiografski je kardijalna zahvaćenost utvrđena kod 39 pacijenata (66,1%); NMR-om kod 16 od 18 pacijenata sa početnim MRI (89%); dok je scintigrafija srca ukazala na Perugini skor 0 i negativan nalaz. Prema Mayo klasifikaciji: 13 pacijenata (21,7%) je bilo u I kliničkom stadijumu (CS), 21 (25%) u II, 16 (26,7%) u IIIa, i 10 (16,7%) u IIIb CS. Hemioterapija (HT) sa alkilirajućim agensima je primenjena kod 24 pacijenta (40%), a bortezomib-HT (Bz-HT) kod 36 (60%). Visokodozna HT sa Melfalanom (HD-Mel) praćena autologom transplantacijom matičnih ćelija hematopoeze (ASCT) je sprovedena kod 10 (16,7%) pacijenata.

Rezultati: Pacijenti lečeni sa Bz-HT imali su značajno bolji hematološki (71,4% vs. 36,4%; $p = 0,013$) i srčani odgovor (70,8% naspram 38,1%; $p = 0,027$) u odnosu na HT sa alkilirajućim lekovima. Značajno bolji hematološki (100% prema 56%; $p = 0,008$) i srčani odgovor (100% naspram 55,6%; $p = 0,017$) je postignut nakon lečenja sa HD-Mel i ASCT, uz postizanje značajno dužeg OS (67,4 vs. 39,5 meseci; $p = 0,036$) u odnosu na terapijski efikasnost standardne HT. Na OS su značajno uticali: Mayo CS ($p < 0,01$), R-Mayo stratifikacija ($p < 0,01$), ASCT podobnosti ($p = 0,05$), hematološki ($p < 0,01$) i srčani odgovor ($p < 0,01$).

Zaključak: Zahvaćenost srca, podobnost za ASCT, hematološki i organski odgovor su osnovni faktori od prognostičkog značaja kod pacijenata sa AL amiloidozom.

Ključne reči: AL amiloidoza, lečenje, prognoza

ABSTRACT

Introduction: AL amyloidosis is a plasma cell dyscrasia with cardiac involvement in 80% of patients.

Objective: was to analyze diagnostic tools and prognostic significance of cardiac involvement.

Methods: The study included 60 patients (January 2015 – June 2023); male/female 30/30, mean age 59 years, 29–77 years. Cardiac involvement was present in 51 patients (85%). Echocardiography showed signs of amyloidosis in 39 patients (66.1%), MRI in 16 of 18 patients with initial MRI (89%), with late gadolinium enhancement (LGE) in 12 patients (75%) and increase extracellular volume (ECV) in 14 patients (87.5%). All patients with scintigraphy with 99mTc-hexamethylenetriamine pyrophosphate had Perugini score 0 (negative). According to the Mayo staging system, I clinical stage (CS) was found in 13 patients (21.7%), II in 21 (25%), IIIa CS in 16 (26.7%), IIIb in 10 (16.7%). Treatment was applied with alkylating based combos in 24 patients (40%), and bortezomib (Bz) based triplets in 36 patients (60%). HD-Melfalan+ASCT was performed in 10 patients (16.7%).

Results: Patients treated with Bz had significantly better hematological (71.4% vs. 36.4%; $p = 0.013$), and cardiac response (70.8% vs. 38.1%; $p = 0.027$). HD-Melfalan+ASCT treated patients showed significantly better hematological (100% vs. 56%; $p = 0.008$) and cardiac response (100% vs. 55.6%; $p = 0.017$). HD-Melfalan+ASCT resulted with significantly longer OS (67.4 vs. 39.5 months; $p = 0.036$). OS was strongly influenced by Mayo CS ($p < 0.01$; HR 1.79, 95% CI 1.17–2.73), R-Mayo stratification ($p < 0.01$; HR 1.80, 95% CI 1.23–2.64), ASCT eligibility ($p = 0.05$; HR 0.29, 95% CI 0.08–1.00), hematologic ($p < 0.01$; HR 0.15, 95% CI 0.07–0.35), cardiac response ($p < 0.01$; HR 0.13, 95% CI 0.05–0.31).

Conclusion: Cardiac involvement, ASCT eligibility, hematologic and organ response have prognostic impact in AL patients.

Keywords: AL amyloidosis, treatment, prognosis

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AMYLOIDOSIS: FROM DIAGNOSIS TO STABLE REMISSION

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SAŽETAK

Uvod: Amiloidoza je monoklonalni plazma-ćelijski poremećaj karakterisan taloženjem abnormalnog proteina, amiloida, u vanćelijskom prostoru različitih tkiva, sa posledičnom multiorganskom disfunkcijom. Amiloid nastaje od rastvorljivih proteina koji se abnormalno preklapaju i talože. Kliničke manifestacije uključuju nespecifične simptome kao i znake zahvaćenosti specifičnih tkiva i organa. Dijagnoza se može postaviti biopsijom zahvaćenog tkiva, a najjedostavnija je biopsija potkožnog masnog tkiva koja je pozitivna na Kongo crveno u 85% slučajeva. Biopsija koštane srži je neophodna za detekciju plazma ćelijske infiltracije (plazmociti < 10%). Amiloidoza se javlja se u dva oblika, sistemska i lokalizovana, najčešća je amiloidoza lakih lanaca (kapa ili lambda lanci).

Prikaz slučaja: Bolesnica stara 59 godina hospitalizovana je zbog disfoničnih smetnji. Laringoskopijom su otkriveni depoziti na glasnim žicama i hirurški su odstranjeni. Patohistološki nalaz je ukazao na amiloidozu larinksa, pa je bilo neophodno utvrditi da li se radi o izolovanoj ili sistemskoj amiloidozi. Dijagnostička obrada nije ukazala na promjene u organima. Registrovana je granična bubrežna funkcija (sCr 94, cCr 91 ml/min, proteinurija 0,09 g/L), povišene vrijednosti LDH (246 IU/L), CK (234 IU/L). Elektroforeza proteina seruma nije ukazala na abnormalnosti, nije dokazana M komponenta imunofiksacijom, imunoelektroforezom nijesu nađena odstupanja (kapa 2,12 mg/L, lambda 1,07 mg/L). Biopsija koštane srži (imunohistohemija, Kongo crveno bojenje) potvrdila je amiloidozu sa 3–5% plazmocita. Postavljena je dijagnoza AL amiloidoze i započeto liječenje CyBorDex protokolom (šest ciklusa). Nakon toga, obavljena je transplantacija koštane srži što je dovelo do dugotrajne i stabilne remisije.

Zaključak: Ranom dijagnostikom amiloidoze izbjegavaju se multiorganska oštećenja, omogućava se primjena agresivne terapije i poboljšava preživljavanje oboljelih.

Ključne reči: amiloidoza, CyBorDex, transplantacija matičnih ćelija

ABSTRACT

Introduction: Amyloidosis is a monoclonal plasma cell disorder characterized by the deposition of an abnormal protein, amyloid, in the extracellular space of various tissues, leading to multi-organ dysfunction. Clinical manifestations include nonspecific symptoms and signs of specific tissue and organ involvement. Diagnosis usually involves biopsy of the affected tissue, the simplest being subcutaneous fat tissue biopsy, which is Congo red-positive in 85% of cases. Bone marrow biopsy is necessary for detecting plasma cell infiltration (plasmocytes < 10%). Amyloidosis occurs in systemic and localized forms, with light-chain amyloidosis (kappa or lambda chains) being the most common.

Case report: A 59-year-old female patient was admitted to the hospital with dysphonic symptoms. Laryngoscopy revealed deposits on vocal cords, which were surgically removed. The histopathological findings indicated laryngeal amyloidosis, so it was necessary to determine whether it was isolated or systemic. Diagnostics did not indicate any changes in the organs. Borderline renal function (sCr 94, cCr 91 ml/min, proteinuria 0.09 g/L) and elevated LDH (246 IU/L) and CK (234 IU/L) were registered. Serum protein electrophoresis showed no abnormalities, and immunofixation did not detect an M component. Immunoelectrophoresis showed no deviations (kappa 2.12 mg/L, lambda 1.07 mg/L). Bone marrow biopsy confirmed amyloidosis with 3–5% plasmocytes. Diagnosis of AL amyloidosis was made and treatment with CyBorDex protocol (six cycles) was initiated. Subsequently, a bone marrow transplant was performed, leading to stable, long-term remission.

Conclusion: Early diagnosis of amyloidosis prevents multi-organ damage, allows for application of aggressive therapy and improves patient survival.

Keywords: amyloidosis, CyBorDex, stem cell transplantation

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EXPRESSION PATTERN OF LONG NON-CODING RNA GAS5 IN PLASMA SAMPLES AND BONE MARROW MONONUCLEAR CELLS FROM MULTIPLE MYELOMA PATIENTS: PRELIMINARY RESULTS

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SAŽETAK

Uvod: GAS5 (transkript 5 specifičan za zaustavljanje rasta) je duga nekodirajuća RNK koja ima ulogu u patogenezi mnogih malignih oboljenja. Međutim, klinički značaj ekspresije GAS5 u multiplom mijelomu (MM) nije ispitan.

Cilj: Određivanje nivoa ekspresije GAS5 kod pacijenata sa MM i analiza njegove povezanosti sa kliničkim i laboratorijskim karakteristikama, prognostičkim skorovima, terapijskim odgovorom (ORR), vremenom do progresije bolesti (PFS) i ukupnim preživljavanjem (OS).

Metode: U istraživanje je uključeno 36 pacijenata sa MM koji su dijagnostikovani u Kliničko-bolničkom centru (KBC) „Bežanijska kosa“ i KBC „Zemun“ u periodu od novembra 2022. do maja 2024. godine. Analiza je urađena na 63 uzorka: (36 uzoraka plazme i 27 uzoraka aspirate koštane srži) i 10 kontrola. Ekspresija GAS5 je detektovana metodom kvantitativne RT-PCR, korišćenjem TaqMan hemije. Analiza relativne GAS5 ekspresije je rađena pomoću komparativne ddCt metodologije.

Rezultati: U grupi je bilo 23 (63,8%) muškarca i 13 žena (36,2%). 24 (66,6%) pacijenta je bilo starije od ≥ 65 godina. Visokorizične citogenetske aberacije su registrovane kod 13 (36,1%) pacijenata. Povoljan terapijski odgovor je postignut kod 17 (62,96%), a kod 9 pacijenata lečenje je u toku. Ekspresija GAS5 u plazmi i koštanoj srži pacijenata sa MM je značajno niža u odnosu na kontrolne uzorke ($p = 0,04$; $p < 0,001$). Međutim, nije pronađena povezanost između ekspresije GAS5 i kliničkih karakteristika, prognostičkih skorova, ORR, PFS i OS.

Zaključak: Snižen nivo ekspresije GAS5 ukazuje na njegovu ulogu u patogenezi MM. Rezultati ukazuju da nivo njegove ekspresije nema uticaja na prognozu bolesnika sa MM, ali za donošenje definitivnih zaključaka neophodno je sprovesti dalja istraživanja na većoj grupi bolesnika.

Ključne reči: multipli mijelom, GAS5, duga nekodirajuća RNK

ABSTRACT

Introduction: GAS5 (growth arrest-specific 5 transcript) is a long non-coding RNA known to play a role in the pathogenesis of many malignant diseases. However, the significance of GAS5 expression in multiple myeloma (MM) has not been investigated.

Objective: To determine the expression levels of GAS5 in MM patients and analyze its association with clinical and laboratory characteristics, prognostic scores, overall response rate (ORR), progression-free survival (PFS) and overall survival (OS).

Methods: The study included 36 MM patients diagnosed at the Clinical Hospital Center (CHC) Bežanijska kosa and CHC Zemun between November 2022 and May 2024. A total of 63 samples were analyzed: 36 plasma samples, 27 bone marrow samples, and 10 controls. GAS5 expression was detected using quantitative RT-PCR with TaqMan chemistry. Relative GAS5 expression analysis was performed using comparative ddCt methodology.

Results: The study group consisted of 23 (63.8%) males and 13 (36.2%) females. Twenty-four patients (66.6%) were aged 65 years or older. High-risk cytogenetic abnormalities were observed in 13 (36.1%) patients. Favorable treatment response was achieved in 17 (62.96%) patients, with 9 patients still undergoing treatment. GAS5 expression in plasma and bone marrow of MM patients was significantly lower compared to control samples ($p = 0.04$; $p < 0.001$). However, no association was found between GAS5 expression and clinical characteristics, prognostic scores, ORR, PFS or OS.

Conclusion: Reduced GAS5 expression indicates its role in MM pathogenesis. The results suggest that GAS5 expression levels do not influence the prognosis of MM patients, but further research on a larger patient cohort is necessary to draw definitive conclusions.

Keywords: multiple myeloma, GAS5, long non-coding RNA

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DARATUMUMAB IN THE TREATMENT OF RELAPSED/REFRACTORY MULTIPLE MYELOMA – A SINGLE CENTER EXPERIENCE

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SAŽETAK

Uvod: Iskustva sa kombinacijama daratumumaba u terapiji relaps/refraktarnog multiplog mijeloma (R/R MM) iz svakodnevne kliničke prakse su ograničena, naročito u zemljama sa limitiranom dostupnošću lekova u terapiji MM. U Srbiji je daratumumab dostupan od 2021. godine pod posebnim uslovima, a od maja 2024. godine nalazi se na pozitivnoj listi RFZO.

Cilj: Prikazujemo iskustvo Instituta za onkologiju i radiologiju Srbije (IORS) sa daratumumabom u lečenju R/R MM.

Metode: Podaci su dobijeni retrospektivno iz istorija bolesti pacijenata.

Rezultati: U retrospektivnu analizu uključeno je 8 pacijenata lečenih od R/R MM na IORS u periodu 2021–2024. godine. Medijana starosti iznosi 57 godina (opseg 53–68), sa ženskom polnom predominacijom (62,5%). Polovina pacijenata imala je R-ISS skor 3. Visokorizična citogenetika utvrđena je kod 33% pacijenata, bubrežna insuficijencija kod 25%, dok je 37,5% pacijenata imalo ekstramedularnu bolest. Rani relaps imalo je 75% pacijenata, refraktornu bolest 33%. Polovina pacijenata je daratumumab primalo u trećoj liniji lečenja, druga polovina u kasnijim linijama. DaraVd protokolom lečeno je 62,5% pacijenata, od kojih je 80% inicijalno tretirano imunomodulatorom sa stopom refraktornosti od 60%. DaraRd protokolom lečeno je 37,5% pacijenata od kojih su svi prethodno lečeni bortezomibom. Medijana trajanja terapije je 7 meseci (1–20), a parcijalna remisija kao najbolji terapijski odgovor postignuta je kod polovine pacijenata. Medijana vremena bez progresije bolesti iznosi 10,5 meseci (1–28). Ukupni odgovor (ORR) iznosi 50%.

Zaključak: Daratumumab u terapiji R/R MM značajno poboljšava ishode lečenja i omogućava uvođenje novih modaliteta u narednim relapsima. Potrebne su prospektivne i opširnije studije realne kliničke prakse sa upotrebom daratumumba u lečenju MM u Srbiji.

Cljučne reči: relaps/refraktorni multipli mijelom, daratumumab

ABSTRACT

Introduction: Experiences with daratumumab combinations in treating relapsed/refractory multiple myeloma (R/R MM) are limited, particularly in regions with restricted access to therapies. In Serbia, daratumumab has been available since 2021 under limited terms.

Objective: We present the experience of the Institute of Oncology and Radiology of Serbia (IORS) with daratumumab in the treatment of R/R MM.

Methods: Data were obtained retrospectively from patients medical records.

Results: Retrospective data from eight R/R MM patients treated at IORS from 2021 to 2024 reveal a median age of 57 years (range 53–68), with a predominance of females (62.5%). Half of these patients had R-ISS score of 3. High-risk cytogenetics were identified in 33% of patients, renal insufficiency in 25%, and 37.5% had extramedullary disease. Early relapse occurred in 75% of patients, and 33% had refractory disease. Half of the patients received daratumumab in the third line of treatment, while the other half received it in subsequent lines. Treatment protocols included DaraVd in 62.5% of cases, where 80% had prior immunomodulator treatment with 60% refractoriness rate, and DaraRd in 37.5%, all previously treated with bortezomib. Median therapy duration was 7 months (1–20), achieving partial remission in half of the patients. Median progression-free survival is 10.5 months (1–28). The overall response rate (ORR) was 50%.

Conclusion: Daratumumab demonstrates significant efficacy in treating R/R MM, facilitating innovative approaches in subsequent relapses. Further prospective studies are crucial to validate these findings and optimize clinical practice in Serbia's MM treatment landscape.

Keywords: relapsed/refractory multiple myeloma, daratumumab

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TREATMENT OF PATIENTS DIAGNOSED WITH MULTIPLE MYELOMA UNFIT FOR TRANSPLANTATION

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SAŽETAK

Uvod: Poslednje decenije liječenja multiplog mijeloma obilježilo je poboljšanje preživljavanja bez progresije (PFS) i ukupnog preživljavanja (OS) pacijenata, vezano za uvođenje novih agenasa. Nekoliko studija je pokazalo marginalniju korist kod starije populacije nepodobne za transplantaciju. To bi se moglo objasniti većom stopom komorbiditeta i disfunkcije organa povezanih sa starenjem.

Prikaz slučaja: Predstavljamo vam pacijenta starog 82 godine koji se prezentovao lakim zamaranjem. Godinu dana unazad liječen je od infarkta miokarda, kada su implantirana 2 stenta, ima aatrijalnu fibrilaciju, hipertenziju i hiperlipoproteinemiju. Dopunskom obradom postavljena je dijagnoza multiplog mijeloma IIIA CS, IgG kappa tipa. Pacijent je u grupi visokog rizika R-ISS skora. ECOG performans status pacijenta je bio 1, Charlson komorbiditetni indeks 5, a skor krhkosti 2. Liječen je po Dara VMP protokolu (daratumumab, bortezomib, melfalan, prednizon), nakon 2 ciklusa liječenja postignuta je remisija bolesti koja se održava 24 mjeseca.

Zaključak: U kontekstu optimizacije terapijskog pristupa potrebno je uz procjenu prognostnog profila, sagledati i liječiti komorbiditete, napraviti detaljnu procjenu krhkosti pacijenta. Aktuelne ESMO smjernice za pacijente koji nisu podobni za jednu od stri preferirana režnima predlaže DaraVMP protokol. U kliničkoj praksi na primjeru našeg pacijenta na primjenu navedenog modaliteta liječenja se postigla rana remisija, uz održavanje remisije 24 mjeseca.

Ključne reči: multipli mijelom, liječenje starijih, daratumumab

ABSTRACT

Introduction: The last decades of multiple myeloma treatment have been marked by the improvement of progression-free survival (PFS) and overall survival (OS) of patients, related to the introduction of new agents. Several studies have shown a more marginal benefit in the elderly population ineligible for transplantation. This could be explained by the higher rate of comorbidities and organ dysfunction associated with aging.

Case report: We present to you an 82-year-old patient who presented with easy fatigue. A year ago he was treated for myocardial infarction when 2 stents were implanted, he has atrial fibrillation, hypertension, and hyperlipoproteinemia. Additional work-up established the diagnosis of multiple myeloma IIIA CS, IgG kappa type. The patient is in the high-risk group of the R-ISS score. The ECOG performance status of the patient was 1, the Charlson comorbidity index was 5, and the frailty score was 2. He was treated according to the Dara VMP protocol (daratumumab, bortezomib, melphalan, prednisone), after 2 cycles of treatment, remission of the disease was achieved, which was maintained for 24 months.

Conclusion: In the context of optimizing the therapeutic approach, it is necessary to evaluate the prognostic profile, look at and treat comorbidities, and make a detailed assessment of the patient's fragility. Current ESMO guidelines for patients who are not eligible for one of the surgically preferred surgical procedures suggest the DaraVMP protocol. In clinical practice, our patient achieved an early remission with maintenance of remission for 24 months.

Keywords: multiple myeloma, treatment of the elderly, daratumumab

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PROGNOSTIC SIGNIFICANCE OF 1q21 CHROMOSOMAL ABNORMALITIES IN MULTIPLE MYELOMA

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SAŽETAK

Uvod: Prognostički značaj specifičnih hromozomskih abnormalnosti (CA) u multiplom mijelomu još uvek predstavlja predmet stručnih razmatranja.

Cilj je bio analiza prognostičkog značaja različitog broja kopija hromozoma 1q21 pri dijagnozi multiplog mijeloma (NDMM).

Metode: Istraživanjem je obuhvaćeno 328 NDMM u periodu od 2017–2023. Prema drugoj Reviziji ISS skora (R2-ISS): R2-ISS1 je imalo 84 (25,6%), R2-ISS2 75 (22,9%), R2-ISS3 152 (46,3%), a R2-ISS4 17 bolesnika (5,2%). Kod 76 od 225 bolesnika sa FISH nalazima (33,7%), trizomija 1q21 (+1q21) je utvrđena kod 28 bolesnika (12,4%), a amplifikacija (amp1q21) kod 48 (21,3%). Double i triple-hit (DTH) MM je utvrđen kod 16 bolesnika (4,9%). Autologa transplantacija matičnih ćelija hematopoeze (ASCT) je sprovedena kod 87 bolesnika (26,5%).

Rezultati: Povoljan terapijski odgovor (ORR $\geq$ PR) je postignut kod 273 bolesnika (86,3%). Nije bilo značajne razlike u ORR između bolesnika sa +1q21 ($p = 0,113$) ili amp1q21 ($p = 0,757$) u poređenju sa bolesnicima bez 1q21 CA. Bolesnici bez 1q21 CA su imali značajno duži PFS u poređenju sa bolesnicima sa +1q21 ili amp1q21 ($p = 0,000$). Bolesnici sa amp1q21 imali su značajno kraći OS u poređenju sa onima koji su imali +1q21 ili su bili bez 1q21 CA ($p = 0,043$). PFS bolesnika sa DTH MM je bio značajno kraći u poređenju sa bolesnicima sa 1q21 CA ($p = 0,000$). Na OS je najviše uticala podobnost za ASCT ($p = 0,000$).

Zaključak: Nalazi amp1q21 i DTH MM značajno utiču na tok mijeloma. Prognostički značaj podobnosti za ASCT ukazuje na potrebu za intenzivnijim pristupom lečenju, uključujući nove imunološke i ćelijske terapije.

Ključne reči: multipli mijelom, 1q21, prognoza

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ABSTRACT

Introduction: The prognostic significance of chromosomal abnormalities (CA) in multiple myeloma is still a subject of expert discussion.

Objective: To analyze prognostic significance of 1q21 in newly diagnosed multiple myeloma (NDMM) patients.

Methods: We analyzed 328 NDMM patients, diagnosed during period 2017–2023. According to Revised-ISS: R-ISS1 was present in 92 patients (28.0%), R-ISS2 in 201 (61.3%), R-ISS3 in 35 patients (10.7%). Regarding R2-ISS, R2-ISS1 had 84 patients (25.6%), R2-ISS2 75 (22.9%), R2-ISS3 152 (46.3%), and R2-ISS4 17 patients (5.2%). In 76 of 225 patients with FISH findings (33.7%), gain1q21 had 28 (12.4%) and amp1q21 48 patients (21.3%). Double and triple-hit (DTH) MM was observed in 16 patients (4.9%). Autologous stem cell transplantation (ASCT) was performed in 87 patients (26.5%).

Results: Overall response rate (ORR $\geq$ PR) was achieved in 273 patients (86.3%). There was no significant difference in ORR between patients with gain1q21 ($p = 0.113$) or amp1q21 ($p = 0.757$) in comparison to the patients without 1q21. Patients without 1q21 had significantly longer PFS in comparison to the patients with gain1q21 or amp1q21 ($p = 0.000$). Patients with amp1q21 had significantly shorter OS in comparison to the patients with gain1q21 or without 1q21 ($p = 0.043$). The PFS of patients with DTH MM was significantly shorter in comparison to the patients with 1q21 CAs ($p = 0.000$). The OS was mostly influenced by ASCT eligibility ($p = 0.000$).

Conclusion: Amplification of 1q21 and DTH MM have the impact on the course of disease. Significance of ASCT eligibility indicates necessity for intensive treatment, immune and cellular therapies.

Keywords: multiple myeloma, 1q21, prognosis

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MIJELOPROLIFERATIVNE NEOPLAZME

MYELOPROLIFERATIVE NEOPLASMS

ZNAČAJ KLINIČKIH I LABORATORIJSKIH PARAMETARA KOD BOLESNIKA SA ESENCIJALNOM TROMBOCITEMIJOM U PROGRESIJI U POSTESENCIJALNU TROMBOCITEMIJSKU MIJELOFIBROZU

IMPACT OF CLINICAL AND LABORATORY FEATURES ON TRANSFORMATION IN POST-ESSENTIAL THROMBOCYTHAEMIC MYELOFIBROSIS FROM ESSENTIAL THROMBOCYTHAEMIA

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SAŽETAK

Uvod: Određeni broj bolesnika sa esencijalnom trombocitemijom (ET) tokom lečenja progredira u posteencijalnu trombocitemijsku mijelofibrozu (post-ET MF).

Cilj: Utvrditi kliničke i laboratorijske parametre koji mogu ukazivati na transformaciju ET u MF.

Metode: Istraživanje je sprovedeno retrospektivnom analizom podataka bolesnika sa ET u Kliničkom centru Vojvodine od 1998–2024. godine. Analizirani su dužina trajanja ET, trombozne komplikacije, prethodno lečenje i krvna slika 12 meseci pre progresije u MF.

Rezultati: Od ukupno 159 bolesnika sa ET, kod 13 (8,18%) je dijagnostikovana post-ET MF tokom prosečnog praćenja 178,75 meseci. Prosečna starost pri obojevanju od ET je bila 53,4 (18–81) godina, u grupi bolesnika sa ET u odnosu na 50,2 (23–65) u grupi post-ET MF, $p = 0,36$. Prosečan perioda praćenja u grupi sa ET je bio 86,7 (13–312) meseci, a u grupi post-ET MF 125,5 (48–276), $p = 0,12$. Između grupa obolelih od ET i post-ET MF nije dokazana statistički značajna razlika u polu, učestalosti JAK2V617F mutacije, tromboznih komplikacija, lečenja hidrokortikoidom, broju leukocita i trombocita. Prosečan nivo hemoglobina i hematokrita je bio 139,99 g/L, odnosno 0,43 u grupi bolesnika sa ET, u odnosu na 110,26 g/L i 0,33 u grupi bolesnika sa post-ET MF ($p = 0,00$ i $p = 0,002$). Univarijantnom logističkom regresijom, na transformaciju u MF uticali su dužina lečenja od ET, niže vrednosti hemoglobina i hematokrita. U multivarijantnoj analizi, niža vrednost hematokrita uticala je na transformaciju u MF.

Zaključak. Tokom praćenja i lečenja bolesnika sa ET, pažnju treba usmeriti na bolesnike sa nižim vrednostima hematokrita koji su mogući kandidati za transformaciju u MF.

Ključne reči: esencijalna trombocitemija, mijelofibroza, Janus kinaza 2

ABSTRACT

Introduction. During the course of essential thrombocythaemia (ET), a certain number of patients will progress into post-essential thrombocythaemic (post-ET) myelofibrosis (MF).

Objective: To determine clinical and laboratory parameters that influence transformation in MF from ET.

Methods: The research included a retrospective analysis of patients with ET in the Clinical Center of Vojvodina between 1998 and 2024. We analyzed the duration of ET, thrombotic complications, treatment modality, and complete blood count 12 months before progression in post-ET MF.

Results: The total number of analyzed patients with ET was 159, and 13 (8.18%) developed post-ET MF during an average period of 178.75 months. The average age at diagnosis ET was 53.4 (18–81) years in the ET group and 50.2 (23–65) in the post-ET MF group, respectively, $p = 0.36$. The average follow-up in the group of ET was 86.7 (13–312) months and 125.5 (48–276) in the postET group, respectively, $p = 0.12$. There were no statistically significant differences between gender, frequency of JAK2V617F mutation, thrombotic complications, hydrocortisone treatment, leukocytes and platelets number in groups. Average hemoglobin level and hematocrit were 139.99 g/L and 0.43 in group patients with ET, and 110.26 g/L and 0.33 in group patients with post-ET MF ($p = 0.00$ i $p = 0.002$). According to univariate logistic regression, duration ET, hemoglobin level, and hematocrit influenced transformation in post-ET MF. Hematocrit was the only parameter that influenced transformation in post-ET MF according to multivariate analysis.

Conclusion: Patients with ET with lower hematocrit level, should be carefully monitored because of possible transformation in MF.

Keywords: essential thrombocythaemia, myelofibrosis, Janus kinase 2

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IMPACT OF CLINICAL AND LABORATORY FEATURES ON TRANSFORMATION IN POST-POLYCYTHEMIC MYELOFIBROSIS FROM POLYCYTHAEMIA VERA

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SAŽETAK

Uvod: Određen broj pacijenata sa pravom policitemijom (PV) tokom života, progredira u postpolicitemijsku mijelofibrozu (post-PV MF).

Cilj: Utvrditi kliničke i laboratorijske parametre koji mogu ukazivati na transformaciju PV u MF.

Metode: Istraživanje je sprovedeno retrospektivnom analizom podataka pacijenata praćenih i lečenih u Kliničkom centru Vojvodine od 1986. do 2024. godine. Analiza je obuhvatila podatke o dužini trajanja PV, trombozne komplikacije, terapijski modalitet i vrednosti krvne slike 12 meseci pre progresije u MF.

Rezultati: Od ukupno 142 bolesnika lečenim zbog prave policitemije, kod 18 (12,67%) bolesnika je dijagnostikovana post-PV MF tokom prosečnog praćenja 91,36 meseci. Prosečna starost pri oboljevanju od PV je bila 62,3 (13–85) godina, u grupi bolesnika sa PV u odnosu na bolesnike sa post-PV MF 51,89 (21–71), $p = 0,002$. Prosečan perioda praćenja u grupi PV je bio 80,45 (8–450) meseci, a u grupi post-PV MF bolesnika 164,67 (24–276), $p = 0,00$. Svi bolesnici sa post-PV MF, 18 (100%) su prethodno lečeni hidroksiureom, za razliku od 79 (64,2%) u grupi PV, $p = 0,005$. Između grupa obolelih od PV i post-PV MF nije dokazana statistički značajna razlika u polu, učestalosti JAK2V617F mutacije, tromboznim komplikacijama i grupama rizika. Univarijantnom logističkom regresijom, na transformaciju u MF uticali su starost pri dijagnozi PV, dužina trajanja PV, vrednosti hemoglobina i hematokrita. U multivarijantnoj analizi, dužina trajanja PV je jedina uticala na transformaciju u MF.

Zaključak: Bolesnici koji se duže vreme prate i leče zbog PV, imaju veći rizik za transformaciju u post-PV MF.

Ključne reči: prava policitemija, mijelofibroza, Janus kinaza 2

ABSTRACT

Introduction: During the course of polycythemia vera (PV), a certain number of patients will progress into post-polycythemic (post-PV) myelofibrosis (MF).

Objective: To determine clinical and laboratory parameters that influence transformation in MF from PV.

Methods: The research included a retrospective analysis of patients with PV in the Clinical Center of Vojvodina between 1986 and 2024. We analyzed the duration of PV, thrombotic complications, treatment modality, and complete blood count values 12 months before progression in post-PV MF.

Results: The total number of analyzed patients with PV was 142, and 18 (12.67%) patients developed post-PV MF during an average period of 91.36 months. The average age at diagnosis PV was 62.3 (13–85) years in the PV group and 51.89 (21–71) in the postPV MF group, respectively, $p = 0.002$. The average follow-up in the group of PV was 80.45 (8–450) months and 164.67 (24–276) in the postPV group, respectively, $p = 0.00$. Of all patients with post-PV MF, 18 (100%) were treated with hydroxyurea, 79 (64.2%) were treated in the PV group, $p = 0.005$. There were no statistically significant differences between gender, frequency of JAK2V617F mutation, thrombotic complications, and risk groups in groups. According to univariant logistic regression, age at diagnosis of PV, duration PV, hemoglobin level, and hematocrit influenced transformation in post-PV MF. Duration of PV was the only parameter that influenced transformation in post-PV MF according to multivariant analysis.

Conclusion: Patients with a long duration and treatment of PV, are at higher risk for transformation in post-PV MF.

Keywords: polycythaemia vera, myelofibrosis, Janus kinase 2

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RUXOLITINIB – SEVEN-YEAR EXPERIENCE OF THE KRAGUJEVAC HEMATOLOGY CLINIC

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SAŽETAK

Uvod: Mijelofibroza je bcr-abl negativna mijeloproliferativna neoplazma koju karakteriše fibroza koštane srži, inefektivna hematopoeza, ekstramedularna hematopoeza, splenomegalija, kraće preživljavanje u odnosu na druge mijeloproliferativne bolesti i progresija abdominalnih i konstitutivnih simptoma. Ruxolitinib je selektivni inhibitor Janus vezane kinaze.

Cilj: Analiza efekata ruxolitiniba u drugoj terapijskoj liniji, kod bolesnika sa primarnom (PMF) i sekundarnom mijelofibrozom različitog DIPSS skora na veličinu slezine.

Metode: Retrospektivna analiza 22 bolesnika sa mijelofibrozom, prethodno lečena hidroksiureom u periodu od 2018. do 01.06.2024. godine. Podaci dobijeni iz pisane medicinske dokumentacije. Veličina slezine određena ehosonografski, određen inicijalni DIPSS skor.

Rezultati: Istraživanjem obuhvaćeno 22 bolesnika prosečne starosti 63,36 (39–77) godina. Bilo je 12 (55%) žena i 10 (45%) muškaraca. PMF je imalo 16 bolesnika, a kod 6 mijelofibroza je nastala transformacijom iz PV (5) i ET (1). Prosečan DIPSS skor 3. U grupi umerenog i visokog rizika bilo je po 11 bolesnika. Prosečno vreme od dijagnoze do uvođenja JAK2 inhibitora: umereni vs. visoki rizik – 5,31 vs. 2,27 godina. Preživeli su imali niži DIPSS skor. Prosek veličine slezine umereni vs. visoki rizik – 195 mm vs. 218 mm bez značajnosti $p > 0,05$. Nema korelacije inicijalne veličine slezine u odnosu na ishod bolesti, $p > 0,05$. Postoji statistički značajnost regresije slezine, nakon 6 meseci umereni vs. visoki rizik – 173,7 mm vs. 151,29 mm i 12 meseci – 176,71 mm vs. 172,20 mm, $p < 0,05$. Bolesnici sa PMF imaju povoljniji ishod na kraju posmatranog perioda – od 16 obolelih preminulo je 5 (31,25%), kod transformacije od 6 preminulo 3 (50%).

Zaključak: Personalizovani pristup, ranije uvođenje ruxolitiniba put je ka uspešnijem kontrolisanju bolesti i usporavanju progresije primarne i sekundarne mijelofibroze.

Ključne reči: ruxolitinib, DIPSS skor, splenomegalija

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ABSTRACT

Introduction: Myelofibrosis is a bcr-abl negative myeloproliferative neoplasm characterized by bone marrow fibrosis, ineffective hematopoiesis, extramedullary hematopoiesis, splenomegaly, shorter survival compared to other myeloproliferative diseases, and progression of abdominal and constitutive symptoms. Ruxolitinib is a selective Janus-linked kinase inhibitor.

Objective: Analysis of the effects of ruxolitinib in the second therapeutic line, in patients with primary (PMF) and secondary myelofibrosis of different DIPSS scores on spleen size.

Methods: Retrospective analysis of 22 patients with myelofibrosis, previously treated with hydroxyurea in the period from 2018 to June 1, 2024. Data obtained from written medical records.

Results: The research included 22 patients with an average age of 63.36 (39–77) years. There were 12 (55%) women and 10 (45%) men. 16 patients had PMF, and in 6, myelofibrosis was caused by transformation from PV (5) and ET (1). There were 11 patients each in the moderate and high risk groups. Average time from diagnosis to introduction of JAK2 inhibitors: moderate vs high risk – 5.31 vs. 2.27 years. Survivors had a lower DIPSS score. Average spleen size moderate vs high risk – 195 mm vs. 218 mm without significance $p > 0.05$. There is a statistically significant regression of the spleen, after 6 months moderate vs high risk – 173.7 mm vs. 151.29 mm and 12 months – 176.71 mm vs. 172.20 mm, $p < 0.05$. Patients with PMF have a more favorable outcome – 5 (31.25%) of 16 patients died, 3 (50%) died out of 6 in secondary myelofibrosis.

Conclusion: Personalized approach, earlier introduction of ruxolitinib is the way to more successful disease control and slowing down the progression of primary and secondary myelofibrosis.

Keywords: ruxolitinib, DIPSS score, splenomegaly

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VALIDATION OF THE TRIPLE A MODEL FOR THE PREDICTION OF SURVIVAL IN 1000 PATIENTS WITH POLYCYTHEMIA VERA

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SAŽETAK

Uvod: Trostruki-A (AAA) model rizika je razvijen za predviđanje OS kod ET bolesnika koji pored starosti (< 50, 0 poena; 50–70, 2 poena; > 70 godina, 4 poena) uključuje visok ANC ($\geq 8 \times 10^9/L$, 1 poen) i nizak ALC (< $1.7 \times 10^9/L$, 1 bod).

Cilj je bio analizirati efikasnost trostrukog-A modela u predviđanju OS kod PV bolesnika.

Metode: Multicentrična retrospektivna studija koja je uključila 1004 PV bolesnika (2005–2022). OS je definisan od dijagnoze do smrti ili posljednje posete.

Rezultati: Medijana praćenja je bila 6 godina (0,3–22), 26,7% je imalo smrtni ishod, OS na 5, 10, 15 godina je bio 83,4%; 62,5%; 44% respektivno. Prvo smo procenili ELN model rizika koji je diskriminisao OS u grupama niskog i visokog rizika sa nedostignutim srednjim OS i 124 m respektivno ($p < 0,001$). Trostruki-A model je takođe efikasno razlikovao OS sa nedostizanjem srednjeg OS, 205, 103 i 80 m u grupi niskog (0–1 poena), umerenog – 1 (3 poena), umerenog – 2 (4 poena) i visokog rizika (5–6 poena) ($p < 0,001$). Druge varijable koje su univarijantno bile povezane sa kraćim OS bile su: starost ≥ 60 godina ($p < 0,001$), $Le \geq 15 \times 10^9/L$ ($p = 0,001$), $ANC \geq 8 \times 10^9/L$ ($p < 0,001$), $ALC < 1.7 \times 10^9/L$ ($p < 0,001$), povišen LDH ($p = 0,048$), HTA ($p < 0,001$), prethodna tromboza ($p = 0,018$). Prilikom postavljanja dijagnoze prisustvo konstitucionalnih ($p = 0,040$), mikrovaskularnih simptoma ($p = 0,013$) i pruritusa ($p = 0,049$) značajno je uticalo na OS. Multivarijantna Cox analiza je potvrdila nezavisni uticaj ELN ($p < 0,001$) i trostrukog-A modela ($p < 0,001$) za predviđanje OS u PV kohorti.

Zaključak: Trostruki-A model se može koristiti za predviđanje OS kod PV bolesnika. Takođe, potrebne su dodatne studije u cilju procene ovog modela u predviđanju razvoja tromboze i transformacije bolesti u PV.

Ključne reči: mijeloproliferativne neoplazme, policitemija vera, prognoza, preživljavanje

ABSTRACT

Introduction: Triple-A (AAA) risk model was developed for OS prediction in ET patients which beside age (<50, 0 points; 50–70, 2 points; > 70 years, 4 points) include high ANC ($\geq 8 \times 10^9/L$, 1 point) and low ALC (< $1.7 \times 10^9/L$, 1 point).

Aim was to analyze the effectiveness of triple-A model in predicting OS of PV-patients.

Methods: Multicenter retrospective study included 1004 PV-patients (2005–2022). The OS was measured from diagnosis until death or the last follow-up visit.

Results: Median follow-up was 6 years (0.3–22), 26.7% died and OS at 5, 10 and 15 years was 83.4%, 62.5% and 44% respectively. We firstly evaluated ELN risk model which discriminated OS in low and high-risk groups with median OS not being reached and 124 m respectively ($p < 0.001$). Triple A model was also able to excellently discriminate OS with median OS not being reached, 205, 103 and 80 m in low (0–1 points), intermediate-1 (3 points), intermediate-2 (4 points) and high-risk-group (5–6 points), respectively ($p < 0.001$). Other variables univariately associated with inferior OS were: age ≥ 60 years ($p < 0.001$), $Le \geq 15 \times 10^9/L$ ($p = 0.001$), $ANC \geq 8 \times 10^9/L$ ($p < 0.001$), $ALC < 1.7 \times 10^9/L$ ($p < 0.001$), elevated LDH ($p = 0.048$), HTA ($p < 0.001$), previous-thrombosis ($p = 0.018$). At diagnosis presence of constitutional ($p = 0.040$), microvascular symptoms ($p = 0.013$) and pruritus ($p = 0.049$) significantly influenced OS. Multivariate Cox analysis confirmed independent impact of ELN ($p < 0.001$) and triple A models ($p < 0.001$) for OS prediction in PV cohort.

Conclusion: Triple-A model may be used for OS prediction in PV patients. Also, additional studies are needed to assess whether the triple-A model may also predict thrombosis and disease transformation in PV.

Keywords: myeloproliferative neoplasms, polycythemia vera, prognosis, survival

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FACTORS ASSOCIATED WITH THROMBOSIS DEVELOPEMNT AND SHORTHER SURVIVAL IN POLYCYTHEMIA VERA

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SAŽETAK

Uvod: Standardni ELN skor u PV baziran na uzrastu i prethodnoj trombozi je nedovoljan i dopuna dodatnim faktorima je neophodna radi preciznije prognoze.

Cilj je utvrditi faktore za razvoj tromboze i kraće preživljavanje (OS) kod PV bolesnika.

Metode: Uključeno je 816 PV bolesnika dijagnostikovanih 2005–2022. i lečenih u UKCS. Analizirani su demografski-kliničko-laboratorijski parametri, indeks komorbiditeta (ACCI) i prisustvo KV faktora u odnosu na razvoj tromboze i OS.

Rezultati: Prosečni uzrast na dijagnozi je bio 62 godine (18–87), sa sličnom raspodelom prema polu. Prethodne tromboze imalo je 22,3% dok je 13,6% bolesnika razvilo trombozu tokom praćenja. Prethodna tromboza ($p = 0,029$), ACCI grupe ($p < 0,001$), prisustvo KV faktora ≥ 1 ($p = 0,001$) i sekundarni malignitet ($p < 0,001$) uticali su na razvoj venske tromboze dok prethodna tromboza ($p = 0,03$), muški pol ($p = 0,006$), ELN skor ($p = 0,001$), ACCI ($p < 0,001$), KV factor ≥ 1 ($p < 0,001$), NLR ≥ 5 ($p = 0,008$) i PLR ≥ 500 ($p < 0,001$) su bli prediktori razvoja arterijske tromboze. U multivarijantnoj analizi, na razvoj venske tromboze uticao je ACCI (HR 3,75; $p < 0,001$), dok na arterijske ACCI (HR 2,12; $p < 0,01$) i PLR ≥ 500 (HR 1,886; $p = 0,028$). Univarijantna analiza identifikovala je faktore povezane sa kraćim OS: starost ≥ 65 godina ($p < 0,001$), $Le \geq 15 \times 10^9/L$ ($p < 0,001$), $ANC \geq 10 \times 10^9/L$ ($p < 0,001$), $Tr \geq 1000 \times 10^9/L$ ($p = 0,027$), sekundarni malignitet ($p < 0,001$), prethodna tromboza ($p = 0,03$), razvoj arterijske ($p < 0,001$) i venske ($p < 0,001$) tromboze tokom praćenja. Multivarijantni Cox-regresioni model utvrdio je uzrast ≥ 65 godina (HR=3,3; $p < 0,001$), ACCI (HR = 1,7; $p < 0,001$) i $ANC \geq 10 \times 10^9/L$ (HR = 1,6; $p = 0,001$) kao najvažnije prediktore OS. Prosečan OS je bio 12,5 godina.

Zaključak: ACCI je potvrđen kao najpouzdaniji prediktor razvoja tromboze i omogućava bolje razgraničenje rizičnih grupa za preživljavanje uz identifikaciju PV bolesnika sa preživljavanjem < 7 godina.

Ključne reči: mijeloproliferativne neoplazme, prognoza, tromboza, preživljavanje

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ABSTRACT

Introduction: ELN score in PV based on age and previous thrombosis is insufficient and identification of additional risk factors for more accurate prognosis is needed.

Objective: to determine factors for thrombosis development and shorter OS in PV.

Methods: Study included 816 PV-patients diagnosed 2005–2022 and treated in UCCS. Demographic-clinical-laboratory parameters, comorbidity index (ACCI) and presence of CV factors in relation to thrombosis development and OS were analysed.

Results: Mean age was 62 years (18–87), with similar distribution by gender. Previous thrombosis had 22.3% patients while 13.6% developed thrombosis during follow-up. Previous thrombosis ($p = 0.029$), ACCI ($p < 0.001$), presence of CV factor ≥ 1 ($p = 0.001$) and secondary malignancy ($p < 0.001$) influenced venous thrombosis development while previous thrombosis ($p = 0.03$), male gender ($p = 0.006$), ELN score ($p = 0.001$), ACCI ($p < 0.001$), CV factor ≥ 1 ($p < 0.001$), NLR ≥ 5 ($p = 0.008$) and PLR ≥ 500 ($p < 0.001$) were predictors of arterial thrombosis development. Multivariate analysis showed that venous development was influenced by ACCI ($p < 0.001$), while arterial with ACCI ($p < 0.01$) and PLR ≥ 500 ($p = 0.028$). Univariante analysis identified factors associated with shorter OS: age ≥ 65 years ($p < 0.001$), $Le \geq 15 \times 10^9/L$ ($p < 0.001$), $ANC \geq 10 \times 10^9/L$ ($p < 0.001$), $Plt \geq 1000 \times 10^9/L$ ($p = 0.027$), secondary malignancy ($p < 0.001$), previous thrombosis ($p = 0.03$), development of arterial ($p < 0.001$) and venous ($p < 0.001$) thrombosis. The most important OS predictors by multivariate Cox model were age ≥ 65 years ($p < 0.001$), ACCI ($p < 0.001$) and $ANC \geq 10 \times 10^9/L$ ($p = 0.001$). Median OS was 12.5 years.

Conclusion: ACCI was most reliable predictor of thrombosis development and allows better delineation of survival risk groups while identifying PV patients with survival < 7 years.

Keywords: myeloproliferative neoplasms, prognosis, thrombosis, survival

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COEXISTENCE OF MYELOPROLIFERATIVE AND LYMPHOPROLIFERATIVE NEOPLASMS: CHALLENGE IN A CLINICAL PRACTICE

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SAŽETAK

Uvod: Pojava evolucije mijeloproliferativnih neoplazmi (MPN) i limfoproliferativnih neoplazmi (LPN) je poznata ali učestalost koegzistencije MPN/LPN je retka.

Cilj je analizirati karakteristike bolesnika sa koegzistencijom MPN/LPN tokom dužeg praćenja.

Metode: Dijagnostikovano je 14 bolesnika sa MPN/LPN koegzistencijom i lečeno u univerzitetskom centru tokom dve decenije.

Rezultati: Srednji uzrast na dijagnozi je bio 53 godine (22–69). Više od 50% bolesnika je imalo prvu dijagnozu MPN dok je 21,5% LPN i kod 21,5% su MPN/LPN postavljene istovremeno. PV i HLL su najčešće bili udruženi (36%). Bolesnici sa MPN i potom razvojem LPN imali su kraći period razvoja drugog maligniteta i agresivniji tok LPN koji može imati fatalni ishod. Mutaciju JAK2V617F imalo je 2/3, dok citogenetske abnormalnosti 1/3 bolesnika najčešće u LPN i potom bolesnici sa koegzistencijom MPN/LPN. Ukupno 57% MPN bolesnika je zahtevalo lečenje bolesti dok 64,3% LPN bolesnika. Bolesnici sa MPN/LPN imali su značajno veći trombotički potencijal (42,8%) i veću učestalost pojave trećeg maligniteta (21,4%) u odnosu na one sa jednim malignitetom. Medijana praćenja bila je 7,5 godina u celoj grupi. Tokom praćenja, 35% pacijenata je imalo smrtni ishod zbog progresije LPN (2 bolesnika), SI (1 bolesnik), HBI (1 bolesnik) i COVID-19 (1 bolesnik).

Zaključak: Obzirom na mlađi uzrast kod postavljanja dijagnoze MPN savetuje se redovna kontrola pojave limfocitoze ili limfadenopatije kao i progresije organomegalije brže od očekivane za MPN a u cilju blagovremene dijagnoze LPN. Prisustvo molekularno-citogenetskih abnormalnosti kod većine bolesnika ukazuje na moguću genetsku nestabilnost i povećan rizik razvoja višestrukih neoplazmi, čime se povećava rizik razvoja tromboze.

Ključne reči: mijeloproliferativna neoplazma, limfoproliferativna neoplazma, prognoza, tromboza, preživljavanje

ABSTRACT

Introduction: The occurrence of evolution of MPN and LPN is known, but the frequency of coexistence of MPN/LPN is rare.

Objective: Aim is to analyze characteristics of patients with MPN/LPN coexistence during long-term follow-up.

Methods: Study included 14 patients with MPN/LPN coexistence diagnosed and treated in university center within two decades.

Results: Mean age at diagnosis was 53 years (22–69). More than 50% of patients had the first MPN diagnosis, while 21.5% had LPN and 21.5% had MPN/LPN diagnosed simultaneously. PV and CLL were most commonly associated (36%). MPNs patients with subsequent LPN had a shorter period to second malignancy development and more aggressive LPN course that can lead to fatal outcome. JAK2V617F mutation had 2/3 and cytogenetic abnormalities 1/3 of patients, most often in LPN then followed by MPN/LPN coexistence. Overall, 57% of MPN-patients required a myeloid-specific treatment while 64.3% of LPNs-patients were treated. MPN/LPN coexistence showed higher thrombotic potential (42.8%), and higher third malignancy development (21.4%), versus those with sole malignancy. Median follow-up was 7.5 years in the whole group. During follow-up 35% of pts died due to progression of LPNs (2 patients), HF (1 patient), HBI (1 patient) and COVID-19 (1 patient).

Conclusion: Considering younger age at MPN diagnosis, it is recommended to regularly check blood lymphocytosis or lymphadenopathy development and organomegaly progression faster than expected for MPN with the aim of timely LPN diagnosis. The presence of molecular-cytogenetic abnormalities in majority of pts indicates possible genetic instability and increased risk for multiple neoplasms development and elevated thrombotic risk.

Keywords: myeloproliferative neoplasm, lymphoproliferative neoplasm, prognosis, thrombosis, survival

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CLINICAL SCORE FOR ASSESSING THROMBOSIS RISK IN POLYCYTHEMIA
VERA DEVELOPED USING ARTIFICIAL INTELLIGENCE
Thrombo-Vera

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SAŽETAK

Uvod: Tromboza predstavlja glavnu komplikaciju PV što dovodi do značajnog morbiditeta i mortaliteta naglašavajući potrebu za precizno stratifikovanje rizika pacijenata i prilagođavanje terapijskih intervencija.

Cilj: Razvoj i validacija modela za predviđanje rizika od tromboze kod pacijenata sa PV, koristeći napredne statističke metode kako bi se poboljšala tačnost predviđanja i klinička primenljivost.

Metode: Studija je obuhvatila 817 PV bolesnika koji su dijagnostikovani i lečeni na Klinici za hematologiju, UKCS, u periodu od 2000–2023. Bayesian logistički regresioni model sa R2D2 priorima korišćen je za predikciju razvoja tromboze. Projekciona prediktivna selekcija varijabli osigurala je precizan model dok je rezultujući model korišćen je za izradu kliničkog skora.

Rezultati: Medijana praćenja je iznosila 59 meseci. Tromboze su se javile kod 108 pacijenata (13,2%). Grupa sa trombozom imala je viši NLR (4,19 vs. 3,52; $p = 0,009$). PLR je bio granično značajan ($p = 0,079$). Pacijenti sa više KV faktora rizika su bili skloniji trombozi ($p = 0,019$). Mikrovaskularni simptomi, pruritus, splenomegalije i prethodne tromboze bili su češći u grupi sa trombozom ($p = 0,011$, $p = 0,019$, $p = 0,002$ i $p = 0,003$, respektivno). Charlson komorbiditetni indeks (CCI) bio je viši u grupi sa trombozom ($p < 0,001$). Finalni model je identifikovao CCI, PLR, splenomegaliju i mikrovaskularne simptome kao ključne prediktore tromboze kod PV. Na osnovu njih je razvijen ThromboVera CS. Vrednost skora 0–1 predstavlja nizak rizik, 2–4 umeren, dok ≥ 5 visok rizik od tromboze. U našoj kohorti, u niskorizičnoj kategoriji 6,94% bolesnika je razvilo trombozu, u umerenoj grupi 15,76% bolesnika dok u visokorizičnoj grupi 48,78% bolesnika.

Zaključak: ThromboVera CS predstavlja jednostavan kliničko-laboratorijski model za predikciju razvoja tromboze kod PV pogodan za svakodnevnu kliničku praksu.

Ključne reči: tromboza, policitemija vera, prediktivni model

ABSTRACT

Introduction: Thrombosis is a major complication of PV, leading to significant morbidity and mortality, emphasizing the need for precise risk stratification of patients and tailored therapeutic interventions.

Objective: Development and validation of a predictive model for thrombosis risk in PV patients using advanced statistical methods to improve prediction accuracy and clinical applicability.

Methods: The study included 817 PV patients diagnosed and treated at the Clinic for Hematology, UCCS, from 2000 to 2023. A Bayesian logistic regression model with R2D2 priors was used to predict the development of thrombosis. Projection predictive variable selection ensured an accurate model, and the resulting model was used to create a clinical score.

Results: The median follow-up was 59 months. Thrombosis occurred in 108 patients (13.2%). The Thrombosis group had a higher NLR (4.19 vs. 3.52, $p = 0.009$). PLR was marginally significant ($p = 0.079$). Patients with more cardiovascular risk factors were more prone to thrombosis ($p = 0.019$). Microvascular symptoms, pruritus, splenomegaly, and previous thrombosis were more common in the Thrombosis group ($p = 0.011$, $p = 0.019$, $p = 0.002$, and $p = 0.003$, respectively). The Charlson Comorbidity Index (CCI) was higher in the Thrombosis group ($p < 0.001$). The final model identified CCI, PLR, splenomegaly, and microvascular symptoms as key predictors. Based on these, ThromboVera CS was developed. Scores 0–1 indicated low risk, 2–4 moderate risk, and ≥ 5 high risk. In our cohort, 6.94% of patients in the low-risk category experienced thrombosis, compared to 15.76% in the moderate-risk group and 48.78% in the high-risk group.

Conclusion: ThromboVera CS is simple clinical-laboratory model for predicting thrombosis development in PV, suitable for everyday clinical practice.

Keywords: thrombosis, polychitemia vera, predictive model

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MIJELOPROLIFERATIVNA NEOPLAZMA SA PDGFRB MUTACIJOM PREZENTOVANA KLINIČKOM SLIKOM HRONIČNE MIJELOMONOCITNE LEUKEMIJE – PRIKAZ SLUČAJA

MYELOPROLIFERATIVE NEOPLASM WITH A PDGFRB MUTATION PRESENTED AS CHRONIC MYELOMONOCYTIC LEUKEMIA – CASE REPORT

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SAŽETAK

Uvod: Prema klasifikaciji hematoloških maligniteta Svetske zdravstvene organizacije 2008. godine kao poseban entitet izdvojene su mijeloproliferativne neoplazme sa abnormalnostima PDGFRA, PDGFRB i FGFR1. Iako klinička slika ovih bolesti može biti raznolika, ipak najčešće se manifestuju leukocitozom i eozinofilijom uz splenomegaliju.

Prikaz slučaja: Pacijentkinja stara 62 godine se javlja hematologu zbog leukocitoze sa dominacijom monocita, anemije i splenomegalije. U inicijalnim nalazima Le 93,6x10⁹/L, neutrofil 48,9%, monociti 43,1%, limfociti 7,4%, eozinofili 0,5%, Hgb 65 g/L, Tr 84x10⁹/L. Biohemijske analize pokazuju povišene vrednosti LDH i mokraćne kiseline. Na UZ stomaka hepatomegalija, jetra 185 mm, i splenomegalija, slezina 204x106x200 mm. Učinjena biopsija koštane srži sugerise na mijeloproliferativnu bolest, najverovatnije CML u fazi akceleracije, dok citogenetske abnormalnosti na konvencionalnoj citogenetici nisu detektovane. RT-PCR na bcr-abl negativan. Protočna citometrija detektuje dominantnu populaciju krupnih monojedarnih ćelija sa karakteristikama monocita i promonocita i izraženom visokom ekspresijom CD4, CD14, CD16, CD33, HLADR, CD65, ali i umerenom ekspresijom CD65. Biopat kostne srži poslat na FISH analizu detektovao je PDGFRB mutaciju u 25% ćelija. Obzirom na inicijanu leukocitozu pacijentkinja najpre započela lečenje hidroksiureom, a zatim i malim dozama imatiniba, koje nije mogla tolerirati obzirom da je uzimanje terapije bilo povezano sa značajnim mučninama i povraćanjem. Pacijentkinja stoga vraćena na terapiju hidroksiureom, ali bez odgovora, te dolazi do letalnog ishoda, 5 meseci nakon postavljanja dijagnoze.

Zaključak: Rano prepoznavanje potrebe za detaljnom citogenetskom i molekularnom obradom ključno je u dijagnostici retkih poremećaja i pravovremenom započinjanju terapije.

Ključne reči: hronična mijelomonocitna leukemija, PDGFB, protočna citometrija

ABSTRACT

Introduction: In the WHO classification of hematological malignancies in 2008, among new entities introduced were myeloproliferative neoplasms with PDGFRA, PDGFRB and FGFR1 abnormalities. Although the clinical appearance of these diseases can be diverse, they are most often manifested by leukocytosis and eosinophilia with splenomegaly.

Case report: A 62-year-old female patient presents to hematologist due to leukocytosis with monocytosis, anemia and splenomegaly. In the initial findings Le 93.6x10⁹/L, neutrophils 48.9%, monocytes 43.1%, lymphocytes 7.4%, eosinophils 0.5%, Hgb 65 g/L, Plt 84x10⁹/L. Biochemical analyzes show elevated LDH and uric acid. Abdominal ultrasound revealed hepatomegaly, liver 185 mm, and splenomegaly, spleen 204x106x200 mm. The performed bone marrow biopsy suggests myeloproliferative disease, most likely CML in the acceleration phase, while on conventional cytogenetics no abnormalities were detected. RT-PCR on bcr-abl is negative. Flow cytometry detects a dominant population consisted of monocytes and promonocytes and high expression of CD4, CD14, CD16, CD33, HLADR, CD65, but also moderate expression of CD65. Biopsy bone marrow sent for FISH analysis detected a PDGFRB mutation in 25% of the cells. In initial treatment patient received hydroxyurea, and then small doses of imatinib, which she could not tolerate, since therapy was associated with significant nausea and vomiting. The patient was therefore returned to hydroxyurea therapy, but without response, and the outcome was fatal, 5 months after the diagnosis.

Conclusion: Early recognition of the need for detailed cytogenetic and molecular processing

is crucial in the diagnosis of rare disorders and the prompt initiation of therapy.

Keywords: chronic myelomonocytic leukemia, PDGFB, flow cytometry

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MYELOPROLIFERATIVE NEOPLASMS IN YOUNGER PATIENTS: A RETROSPECTIVE ANALYSIS OF CLINICAL CHARACTERISTICS

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SAŽETAK

Uvod: Mijeloproliferativne neoplazme se obično dijagnosticiraju kod bolesnika starosti oko 60 godina, međutim u kliničkoj praksi se često sreću bolesnici mlađi < 40 godina.

Cilj: Procena kliničko-laboratorijskih karakteristika, učestalost tromboza i analiza terapijskog pristupa kod bolesnika sa MPN < 40 godina.

Metode: Retrospektivna studija obuhvatila je 84 bolesnika, dijagnostikovanih prema SZO kriterijumima, lečenih na Klinici za hematologiju UKCS od 2000 do 2024.

Rezultati: Medijana starosti iznosila je 33 godine sa većom učestalošću žena (60,7%). PV je nađena kod 61,9%, ET kod 25%, prePMF kod 13,1% ispitanika. Mutacija JAK2V617F je detektovana kod 46,5% bolesnika. Mikrovaskularne simptome imalo je 27,4%, svrab 14,3%, konstitucionalne simptome 7,1%, splenomegaliju 45,2% bolesnika. Najviši hemoglobin i hematokrit su imali PV bolesnici (172 g/L, 51,6%). Broj trombocita je bio najveći u prePMF (1122x10⁹/L), zatim ET (865x10⁹/L) i PV (696x10⁹/L). Raspodela prema stepenu fibroze koštane srži: MF0 – 28,5%, MF1 – 54,8%, MF2 – 4,8%. Ukupno 41,7% je imalo bar jedan kardiovaskularni faktor rizika, najčešće pušenje (23,8%). Prethodne tromboze je imalo 16,7% bolesnika (uglavnom PV). Tromboze tokom praćenja (8,3%) su imali samo PV bolesnici. Aspirin je koristilo 86,9% bolesnika dok su flebotomije primenjene kod skoro svih PV bolesnika. Citoreduktivnom terapijom je lečeno 43,9% bolesnika, 39,1% jednom TL, najčešće HU. Prema ELN skor, 82,1% bolesnika pripada niskom riziku. Medijana praćenja je bila 72 meseca, a dva bolesnika su preminula (2,45%).

Zaključak: Većina mlađih bolesnika sa MPN pripada ELN grupi niskog rizika međutim zbog razvoja tromboze (25%), prisutnih tegoba, stepena trombocitoze i splenomegalije > 18 cm skoro 1/2 prima citoreduktivnu terapiju. To ukazuje na potrebu njihove bolje stratifikacije kao i upotrebu drugačijih metoda za procenu rizika bolesti kao što je to NGS.

Ključne reči: mijeloproliferativne neoplazme, tromboze, adolescenti, mlađi uzrast

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ABSTRACT

Introduction: Myeloproliferative neoplasms are usually diagnosed in patients around 60-year-old, however, in clinical practice, patients < 40 years are often encountered.

Objective: Assessment of clinical-laboratory characteristics, thrombosis incidence and therapeutic approaches in patients with MPN < 40 years.

Methods: Retrospective study included 84 patients, diagnosed according to WHO criteria, treated at Clinic of Hematology, UKCS from 2000–2024.

Results: Median age was 33 years with female predominance (60.7%). PV was found in 61.9%, ET in 25%, prePMF in 13.1% of patients. JAK2V617F mutation was detected in 46.5% patients. Microvascular symptoms were present in 27.4%, pruritus in 14.3%, constitutional symptoms in 7.1%, splenomegaly in 45.2% patients. Highest hemoglobin and hematocrit levels were in PV (172 g/L, 51.6%). Platelet count was highest in prePMF (1122x10⁹/L), then ET (865x10⁹/L) and PV (696x10⁹/L). Distribution according to BM fibrosis: MF0 – 28.5%, MF1 – 54.8%, MF2 – 4.8%. Overall, 41.7% had at least one cardiovascular risk factor, most commonly smoking (23.8%). Previous thrombosis were present in 16.7% patients (mainly PV). Thrombosis during follow-up (8.3%) occurred only in PV patients. Aspirin was used in 86.9% patients, while phlebotomies were used in almost all PV patients. Cyto-reductive therapy was given to 43.9% patients, 39.1% with one TL, usually HU. According to the ELN score, 82.1% patients were low risk. Median follow-up was 72 months, and two patients died (2.45%).

Conclusion: Most younger MPN patients belong to ELN low risk group, however, due to development of thrombosis (25%), symptoms, degree of thrombocytosis and splenomegaly > 18 cm, almost 1/2 receive cyto-reductive therapy. This highlights need for better stratification and alternative risk assessment methods, such as NGS.

Keywords: myeloproliferative neoplasms, thrombosis, adolescents, younger age

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QUALITY OF LIFE OF MYELOFIBROSIS PATIENTS TREATED WITH JAK2 INHIBITORS (RUXOLITINIB) – EXPERIENCE OF OUR CENTER

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SAŽETAK

Uvod: Primena JAK2 inhibitora značajno je unapredila lečenje obolelih od primarne i sekundarne mijelofibroze.

Cilj: Analiza kvaliteta života valorizovana MPN10 skorom obolelih od mijelofibroze lečenih ruksolitininom.

Metode: Istraživanjem je obuhvaćeno 22 bolesnika (12 žena i 10 muškaraca), lečenih u Klinici za hematologiju. Za procenu kvaliteta života korišćen je MPN10 skor (inicijalni, nakon 6, 12, 18 i 24 meseca). Analiza učinjena SPSS 22.0, značajnost $\alpha < 0,05$.

Rezultati: Prosečna starost obolelih u momentu dijagnoze bila je 63,36 godina. Prosečno vreme od postavljanja dijagnoze do uvođenja ruksolitinitiba bilo je 3,7 godina. Prosečna vrednost MPN10 skora pri uvođenju leka bila je 52,68. Nakon 6 meseci terapije, u grupi od 17 bolesnika MPN10 iznosi 28,14, nakon 12 meseci u grupi od 12 bolesnika skor je 26,0. Posle 18 meseci bilo je 9 bolesnika sa prosečnim MPN10 skorom 18,22, a 24 meseca kasnije skor je bio 18,0. Postoji značajna razlika između inicijalnog MPN10 skora i skora posle 6 meseci ($p = 0,001$), kao i razlika MPN10 skora posle 6 i 12 meseci ($p = 0,017$). MPN10 skor nakon 12 i 18 meseci se značajno razlikuje ($p = 0,042$), dok skor nakon 18 i 24 meseca je bez statističke značajnosti ($p = 0,109$). Preminulo je 8, a lečenje je u toku kod 14 bolesnika.

Zaključak: Ispitivanjem je utvrđeno da bolesnici lečeni ruksolitininom pokazuju značajno popravljanje kvaliteta života – smanjenje konstitucionalnih simptoma, maksimum poboljšanja postižu posle 18 meseci terapije i isti održavaju do kraja posmatranog perioda. Uz ograničenje malim uzorkom, ipak se sugerise potreba za detaljnijom evaluacijom konstitucionalnih simptoma u obolelih od mijelofibroze.

Cljučne reči: mijelofibroza, ruksolitinin, MPN10 skor, kvalitet života

ABSTRACT

Introduction: JAK2 inhibitors treatment improved therapy of patients with primary and secondary myelofibrosis.

Objective: To analyze the quality of life, assessed by the MPN10 score in myelofibrosis patients treated with Ruxolitinib.

Methods: The study included 22 patients. MPN10 score was used to assess the quality of life at the beginning of treatment and after 6, 12, 18, and 24 months. Analysis was performed using SPSS 22.0, with significance (α) < 0.05 .

Results: The average time from diagnosis to the initiation of Ruxolitinib treatment was 3.7 years. The average MPN10 score at the start of treatment was 52.68. After 6 months of therapy, in a group of 17 patients, the MPN10 score was 28.14. After 12 months, in a group of 12 patients, the score was 26.0. After 18 months, there were 9 patients with an average MPN10 score of 18.22, and 24 months later, the score was 18.0. There was a significant difference between the initial MPN10 score and the score after 6 months ($p = 0.001$), as well as between the scores after 6 and 12 months ($p = 0.017$). The MPN10 score after 12 and 18 months also showed a significant difference ($p = 0.042$), while the difference between the scores after 18 and 24 months was not statistically significant ($p = 0.109$). Treatment is ongoing for 14 patients.

Conclusion: The study found that patients treated with Ruxolitinib show a significant improvement in quality of life – reduction in constitutional symptoms, the maximum improvement is achieved after 18 months of therapy and is maintained until the end of the observed period.

Keywords: myelofibrosis, ruxolitinib, MPN10 score, quality of life

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PRIMARY AND SECONDARY MYELOFIBROSIS – SIMILARITIES AND DIFFERENCES IN CLINICAL CHARACTERISTICS AND SURVIVAL

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SAŽETAK

Uvod: Mijelofibroza je heterogena klonška mijeloproliferativna neoplazma koja može nastati de novo ili transformacijom iz drugih mijeloproliferativnih neoplazmi.

Cilj: Utvrditi razlike u kliničkim, laboratorijskim i prognoznim činiocima između bolesnika sa primarnom (PMF) i sekundarnom (SMF) mijelofibrozom lečenih ruksolitinitibom.

Metode: Kod bolesnika sa PMF i SMF lečenih ruksolitinitibom u Kliničkom centru Vojvodine, od 2017. do 2024. godine, retrospektivno, korišćenjem medicinske dokumentacije, analizirani su klinički parametri, krvna slika na početku bolesti i DIPSS (Dynamic International Prognostic Scoring System) skor, kao i njihov uticaj na ukupno preživljavanje.

Rezultati: Od ukupno 61 bolesnika, 37 (60,6%) je imalo PMF, a 24 (39,4%) SMF. Intermedijarni 2 i visok rizik prema DIPSS skoru imalo je 28 (75,7%) u grupi sa PMF i 18 bolesnika (75%) sa SMF ($p = 1,0$). Vrednosti hemoglobina, broj leukocita i trombocita, prisustvo transfuzione zavisnosti i veličina slezine nisu pokazali statističku značajnu razliku među grupama. U grupi sa PMF, preminulo je 15 bolesnika (40,5%), a u grupi sa SMF 13 (54,2%) ($p = 0,27$). U grupi sa PMF na kraće preživljavanje je uticalo prisustvo tranfuzione zavisnosti ($p = 0,04$) i splenomegalije koja je 10 cm i veća ispod levog rebarnog luka ($p = 0,006$). U grupi bolesnika sa SMF nisu se izdvojili parametri koji utiču na kraće preživljavanje.

Zaključak: Bolesnici sa PMF i SMF imaju slične kliničke karakteristike i ukupno preživljavanje. Prisustvo transfuzione zavisnosti i splenomegalije su faktori koji utiču na kraće preživljavanje bolesnika sa PMF, ali ne i na dužinu preživljavanja bolesnika sa SMF.

Cljučne riječi: mijelofibroza, preživljavanje, ruksolitinitib

ABSTRACT

Introduction: Myelofibrosis is a heterogeneous clonal myeloproliferative neoplasm that can arise de novo or through the transformation of other myeloproliferative neoplasms.

Objective: To determine the differences in clinical, laboratory, and prognostic factors between patients with primary (PMF) and secondary (SMF) myelofibrosis treated with ruxolitinib.

Methods: In patients with PMF and SMF treated with ruxolitinib at the Clinical Center of Vojvodina from 2017 to 2024, clinical parameters, initial blood counts, and DIPSS (Dynamic International Prognostic Scoring System) scores, as well as their impact on overall survival, were retrospectively analyzed using medical documentation.

Results: Of a total of 61 patients, 37 (60.6%) had PMF, and 24 (39.4%) had SMF. Intermediate-2 and high-risk according to the DIPSS score were present in 28 (75.7%) in the PMF group and 18 patients (75%) in the SMF group ($p = 1.0$). Hemoglobin levels, white blood cell counts, platelet counts, transfusion dependency, and spleen size did not show statistically significant differences between the groups. In the PMF group, 15 patients (40.5%) died, while in the SMF group, 13 (54.2%) died ($p = 0.27$). In the PMF group, shorter survival was influenced by transfusion dependency ($p = 0.04$) and splenomegaly ($p = 0.006$), which is 10 cm and larger below the left rib cage. In the SMF group, no parameters were identified that significantly influenced shorter survival.

Conclusion: Patients with PMF and SMF have similar clinical characteristics and overall survival. The presence of transfusion dependence and splenomegaly are factors influencing shorter survival in PMF patients, but not the survival length in SMF patients.

Keywords: myelofibrosis, survival, ruxolitinib

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EFFICACY OF IMATINIB AS FIRST-LINE THERAPY IN CHRONIC MYELOID LEUKAEMIA: A RETROSPECTIVE STUDY

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SAŽETAK

Uvod: Uvođenje inhibitora tirozin kinaze (TKI) potpuno je promenilo način lečenja hronične mijeloidne leukemije (HML), značajno povećavajući stopu remisija i preživljavanja bolesnika.

Cilj: Procena efikasnosti imatiniba u prvoj terapijskoj liniji (ITL) na osnovu postignutog citogenetskog i molekularnog odgovora kao i dužine preživljavanja bolesnika.

Metode: Ova retrospektivna studija obuhvatila je 331 HML bolesnika sa hroničnom fazom HML dijagnostikovanih prema ELN kriterijumima i lečenih sa Imatinibom 400 mg/dn u Klinici za hematologiju, UKCS.

Rezultati: Terapija imatinibom dovela je do kompletne citogenetske remisije (CCgR) kod 72,8%, major citogenetskog odgovora (major CgR) kod 9,1%, minor citogenetskog odgovora (minor CgR) kod 3,3%, dok 14,2% nije imalo odgovor. Nakon praćenja od 88 meseci, 40,5% je razvilo primarnu ili sekundarnu rezistenciju. Pacijenti koji su reagovali na imatinib su obično imali $Le \leq 120 \times 10^9/L$, blaste u perifernoj krvi $\leq 3\%$, jetru ≤ 15 cm, slezinu ≤ 17 cm ($p < 0,001$) i većinom su pripadali Sokal niskoj grupi rizika ($p = 0,008$). Prediktori preživljavanja su bili postizanje CCgR ($p = 0,001$), procenat blasta u perifernoj krvi ($p = 0,001$) i Hasford skor ($p = 0,008$). Kod bolesnika sa postignutim CCgR, 26,1% je imalo MR3, dok je 73,9% premašilo četverostruko smanjenje BCR-ABL transkripata ($\geq MR4$). Stope preživljavanja za 5, 10 i 15 godina iznosile su 95,7%, 92,5% i 84,2%, respektivno. Stopa mortaliteta je bila 17,8%, pri čemu kod polovine kao posledica HML.

Zaključak: Imatinib u ITL omogućava postizanje CCgR kod 2/3 bolesnika, što je povezano sa desetogodišnjim preživljavanjem preko 90%. Dodatno, 2/3 pacijenata sa CCgR postiže $\geq MR4$. Optimalni kandidati za terapiju imatinibom su oni sa nižim brojem leukocita i blasta, normalnim promerom jetre, manjim promerom slezine koji pripadaju grupi niskog rizika prema Sokal skor.

Ključne reči: hronična mijeloidna leukemija (CML), inhibitori tirozin kinaze (TKI), imatinib, citogenetski odgovor, molekularni odgovor

ABSTRACT

Introduction: The introduction of the tyrosine kinase inhibitors (TKIs) completely changed treatment of chronic myeloid leukemia (CML), significantly increasing rate of remission and patient survival.

Objective: Evaluation of effectiveness of imatinib in first therapeutic line (ITL) based on achieved cytogenetic and molecular response, as well as the length of patient survival.

Methods: This retrospective study included 331 CML patients with chronic phase CML diagnosed according to ELN criteria and treated with Imatinib 400 mg/day at Clinic of Hematology, UCCS.

Results: Imatinib led to complete cytogenetic response (CCyR) in 72.8% of patients, major cytogenetic response (major CyR) in 9.1%, minor cytogenetic response (minor CyR) in 3.3%, and no response in 14.2%. After a median follow-up of 88 months, 40.5% developed primary or secondary resistance. Responders typically had $WBC \leq 120 \times 10^9/L$, blood blast $\leq 3\%$, liver ≤ 15 cm, spleen ≤ 17 cm ($p < 0.001$), and were mainly Sokal low-risk ($p = 0.008$). Survival predictors included CCyR achievement ($p = 0.001$), blood blast percentage ($p = 0.001$), and Hasford score ($p = 0.008$). Among CCyR achievers, 26.1% reached MR3, while 73.9% surpassed a four-log reduction in BCR-ABL transcript levels ($\geq MR4$). The 5, 10, and 15-year survival rates were 95.7%, 92.5%, and 84.2%, respectively. The mortality rate was 17.8%, with half attributable to CML.

Conclusion: Imatinib as a ITL enables the achievement of CCyR in 2/3 of patients, correlating with survival rates over 90% at 10 years. Additionally, 2/3 of patients with CCyR achieve $\geq MR4$. Optimal candidates for imatinib therapy are those with lower leukocyte and blood blast counts, normal liver dimensions, smaller spleen diameter, who belongs to low risks according to Sokal score.

Keywords: chronic myeloid leukemia, tyrosine kinase inhibitors (TKIs), imatinib, cytogenetic response, molecular response

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MYELOPROLIFERATIVE NEOPLASMS AND AUTOIMMUNE DISEASES: CASE REPORT

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SAŽETAK

Uvod: Poznato je da su autoimuna stanja povezana sa povećanim rizikom pojave limfoproliferativnih maligniteta. Etiologija mijeloidnih maligniteta ostaje uglavnom nepoznata.

Prikaz slučaja: Pacijentkinja starosne dobi 63 godine upućena je hematologu zbog eritrocitoze 2023. godine. Tegobe pacijentkinje počinju 2007. godine pojavom bola i otoka sitnih zglobova šaka i stopala uz naizmenično bledilo i modrilo šaka. Dalji tok bolesti karakteriše RF i CRP pozitivnost uz negativan nalaz za CCP, anti SCL 70 i anticentromerna antitela 2009. godine. Inicijalno je lečena terapijom hidroksihlorokin i pronison 10 mg. Dijagnoza primarnog Sjogrenovog sindroma postavljena je 2016. godine nakon pozitivne serologije za anti SSA uz ostale kriterijume bolesti. Evaluacijom bolesti 2020. godine konstatovano da kod pacijentkinje postoji sporo evolutivna forma CREST varijante sistemske skleroze i sekundarni Sicca sindrom KKS oktobar 2023. godine LE 10,5x10⁹/L, HGB 163 g/L, HCT 0,502 L/L, TR0 298,6x10⁹/L. PCR nije pokazao prisustvo V617F u JAK2 genu. Vrednost Epo u serumu bila je 8,3 mU/mL.

Patohistološki nalaz biopsije koštane srži, mikromorfološki nalaz i rezultati histohemijskih i imunohistohemijskih analiza mogli bi ići u prilog dijagnozi mijeloproliferativne neoplazme koštane srži tipa prave policitemije MPN PV. Bolesnica je lečena flebotomijama uz antiagregacionu terapiju.

Zaključak: Rizik pojave specifičnih karcinoma varira zavisno od vremena pojave skleroderme, tipa autoantitela i zahvaćenosti kože. Dijagnoza JAK2 negativne PV u bolesnice sa autoimunim reumatskim oboljenjem ukazuje na potrebu praćenja ovih pacijenata.

Ključne reči: JAK2 mutacija, prava policitemija, sistemska skleroza

ABSTRACT

Introduction: Autoimmune conditions are known to be associated with an increased risk of lymphoproliferative malignancies, while the etiology of myeloid malignancies remains largely unknown.

Case report: A 63-year-old female patient was referred to a hematologist for erythrocytosis in 2023. Her symptoms began in 2007 with pain and swelling in the small joints of the hands and feet, along with alternating paleness and cyanosis of the hands. In 2009, tests showed positive RF and CRP, with negative results for CCP, anti-SCL 70, and anticentromere antibodies. Initially, she was treated with hydroxychloroquine and prednisone 10 mg. In 2016, a diagnosis of primary Sjogren's syndrome was made based on positive serology for anti-SSA along with other disease criteria. In 2020, a slow-evolving form of the CREST variant of systemic sclerosis and secondary Sicca syndrome was noted. Blood tests in October 2023 showed leukocytes 10.5x10⁹/L, hemoglobin 163 g/L, hematocrit 0.502 L/L, and platelets 298.6x10⁹/L. PCR testing did not detect the V617F mutation in the JAK2 gene, and the serum erythropoietin level was 8.3 mU/mL. A bone marrow biopsy suggested a diagnosis of myeloproliferative neoplasm, specifically polycythemia vera (PV). The patient was treated with phlebotomy and antiplatelet therapy.

Conclusion: The risk of specific cancers varies depending on the onset of scleroderma, the type of autoantibodies present, and skin involvement. The diagnosis of JAK2-negative PV in a patient with autoimmune rheumatic disease highlights the need for ongoing monitoring of these patients.

Keywords: JAK2 mutation, polycythemia vera, systemic sclerosis

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UTICAJ TERAPIJE ASPIRINOM NA VREDNOST LEUKOCITNO-TROMBOCITNIH AGREGATA KOD NISKORIZIČNIH BOLESNIKA SA MIJELOPROLIFERATIVNIM NEOPLAZMAMA

THE EFFECT OF ASPIRIN THERAPY ON THE VALUE OF LEUKOCYTE-PLATELET AGGREGATES IN LOW-RISK PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS

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SAŽETAK

Uvod: Dinamičke interakcije između aktiviranih trombocita, leukocita i endotela i stvaranje povećanih nivoa cirkulišućih leukocitno-trombocitnih agregata se smatraju glavnim uzročnicima trombofilnog stanja u mijeloproliferativnim neoplazmama (MPN). Uprkos terapiji prilagođenoj stepenu rizika, značajan procenat bolesnika sa MPN dobija tromboembolijske komplikacije u toku bolesti.

Cilj: Ispitivanje uticaja aspirina na vrednost cirkulišućih neutrofilno-trombocitnih (Ne-Tr) i monocitno-trombocitnih (Mo-Tr) agregata.

Metode: U studiju je uključeno 50 bolesnika sa de novo MPN (24 PV, 15 ET, 11 PMF), sa dijagnozom postavljenom prema standardnim kriterijumima SZO. Bolesnici su stratifikovani u grupu niskog rizika za razvoj tromboembolijskih komplikacija (≤ 60 godina i/ili odsustvo prethodnih tromboza) i lečeni su monoterapijom aspirinom. Prisustvo Ne-Tr i Mo-Tr agregata u perifernoj krvi je ispitivano metodom multiparametarske protočne citometrije odmah nakon dijagnoze MPN, a zatim šest meseci od početka terapije.

Rezultati: U svim podtipovima MPN prosečne vrednosti Ne-Tr i Mo-Tr agregata su pre početka terapije bili povišeni u odnosu na kontrolnu grupu ($p < 0,01$), a zatim su pod uticajem terapije redukovani ($p < 0,01$). Učestalost povišenih vrednosti Ne-Tr i Mo-Tr agregata je posle terapije u celoj grupi MPN bolesnika bila značajno niža u odnosu na dijagnozu (38% vs. 66%; $p = 0,003$ i 10% vs. 42%; $p = 0,001$), sa varijacijama po tipovima MPN (PV: 12,5% vs. 50,0% i 2,5% vs. 33,3%; ET: 66,4% vs. 80,0% i 20,0% vs. 46,6%; PMF: 54,5% vs. 81,8% i 9,1% vs. 54,5%).

Zaključak: Monoterapija aspirinom je rezultirala smanjenjem vrednosti leukocitno-trombocitnih agregata u sve tri grupe bolesnika sa MPN, pri čemu je najbolji odgovor na terapiju aspirinom zabeležen u grupi PV bolesnika.

Ključne reči: mijeloproliferativne neoplazme, leukocitno-trombocitni agregati, aspirin

ABSTRACT

Introduction: Dynamic interactions between activated platelets, leukocytes and endothelium and the generation of increased levels of circulating leukocyte-platelet aggregates are considered to be the main causes of the thrombophilic state in myeloproliferative neoplasms (MPN). **Objective:** Investigating the effect of aspirin on value of circulating neutrophil-platelet (Ne-Plt) and monocyte-platelet (Mo-Plt) aggregates.

Methods: The study included 50 patients with de novo MPN (24 PV, 15 ET, 11 PMF), diagnosed according to standard WHO criteria. Patients were stratified into a low-risk group for the development of thromboembolic complications and were treated with aspirin monotherapy. The presence of Ne-Plt and Mo-Plt aggregates in peripheral blood was investigated by multiparameter flow-cytometry immediately after the diagnosis of MPN, and six months after the start of therapy.

Results: In all subtypes MPN average values of Ne-Plt and Mo-Plt aggregates were higher before the start of therapy compared to the control group ($p < 0.01$), and then, under therapy, they were reduced ($p < 0.01$). The frequency of increased values of Ne-Plt and Mo-Plt aggregates after therapy in the whole group of MPN patients was significantly lower compared to diagnosis (38% vs. 66%; $p = 0.003$ and 10% vs. 42%; $p = 0.001$), with variations by MPN subtypes (PV: 12.5% vs. 50.0% and 2.5% vs. 33.3%; ET: 66.4% vs. 80.0% and 20.0% vs. 46.6%; PMF: 54.5% vs. 81.8% and 9.1% vs. 54.5%).

Conclusion: Aspirin monotherapy resulted in a decrease in the value of leukocyte-platelet aggregates in all three MPN subtypes, where the best response to aspirin therapy was recorded in the PV subtype.

Keywords: myeloproliferative neoplasms, leukocyte-platelet aggregates, aspirin

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EKSTRAMEDULARNA HEMATOPOEZA U SLUZNICI GASTROINTESTINALNOG TRAKTA I DRUGIM ORGANIMA KOD BOLESNICE SA PRIMARNOM MIJELOFIBROZOM – PRIKAZ SLUČAJA

EXTRAMEDULLARY HEMATOPOIESIS IN THE MUCOSA OF THE GASTROINTESTINAL TRACT AND OTHER ORGANS IN A PATIENT WITH MYELOFIBROSIS – CASE REPORT

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SAŽETAK

Uvod: Ekstramedularna hematopoeza u jetri, slezini i limfnim žlezdama, a ređe u drugim organima, jedno je od osnovnih obeležja bolesnika sa mijelofibrozmom.

Prikaz slučaja: Bolesnici staroj 54 godine je 2009. godine postavljena dijagnoza policitemije vere. Lečenje je obuhvatilo primenu flebotomija i antiagregacione terapije, potom hidroksiureje i busulfana. U martu 2022. godine je dokazana transformacija u postpolicitemičnu mijelofibrozu, JAK2V617F pozitivnu, visokog DIPSS (Dynamic International Prognostic Scoring System) i DIPSS plus skora. Tri meseca nakon postavljene dijagnoze, u terapiju je uveden ruxolitinib, sa redukcijom doze zbog hepatotoksičnosti šest meseci nakon početka terapije. U junu 2023. godine, kod bolesnice je sprovedena gastroenterološka dijagnostika, nakon preležanog ileusa. Patohistološki nalaz ukazao je na ekstramedularnu hematopoezu u želudačnoj sluznici (višejedarne džinovske ćelije u lamini propiji, CD31+ i CD61+). Kod bolesnice je u avgustu 2023. došlo je do transformacije mijelofibroze u akutnu mijeloidnu leukemiju, a hospitalni tok se komplikovao enteroragijama, urinarnim infekcijama, urosepsama i psihoorganskim sindromom. Infiltracija sluznice creva ćelijama blastoidnog izgleda (CD117+/-, CD33+, CD38+, CD138+, HLADR+, CD34-) je opisana u biopsatu sluznice kolona. Osim opisanih infiltrata sluznice digestivnog trakta, kod bolesnice je postavljena sumnja na infiltraciju sakruma, VL4 i Th12 pršljenova i predeo spoja frontalne i parijetalne kosti, u okviru ekstramedularne hematopoeze, koja nije patohistološki dokazana. Terapija azacitidinom nije započeta zbog smrtnog ishoda bolesnice.

Zaključak: Ekstramedularna hematopoeza digestivnog trakta može dovesti do životno-ugrožavajućih komplikacija kod bolesnika sa mijelofibrozmom, kao što su krvarenje ili ileus. Kod naše bolesnice, uprkos primeni savremene terapije osnovne bolesti ruxolitinibom, došlo je da nepovoljnog ishoda.

Ključne reči: ekstramedularna hematopoeza, mijelofibroza, prikaz slučaja

ABSTRACT

Introduction: Extramedullary hematopoiesis in the liver, spleen, and lymph nodes, and rarely in other organs, is one of the primary features of patients with myelofibrosis.

Case report: In 2009, a 54-year-old patient was diagnosed with polycythemia vera. Treatment included phlebotomy and antiplatelet therapy, followed by hydroxyurea and busulfan. In March 2022, the disease transformed into post-polycythemic myelofibrosis, JAK2V617F positive, high DIPSS (Dynamic International Prognostic Scoring System), and DIPSS plus score. Three months after diagnosis, ruxolitinib was introduced, but the dose was reduced due to hepatotoxicity six months later. In June 2023, gastroenterological diagnostics were performed following an episode of ileus. Histopathological findings indicated extramedullary hematopoiesis in the gastric mucosa (multinucleated giant cells in the lamina propria, CD31+ and CD61+). In August 2023, the patient's myelofibrosis transformed into acute myeloid leukemia, complicated by enterorrhagia, urinary infections, urosepsis, and psychoorganic syndrome during hospitalization. Infiltration of the intestinal mucosa with blast-like cells (CD117+/-, CD33+, CD38+, CD138+, HLADR+, CD34-) was described in the colon mucosa biopsy. Besides these infiltrations of the digestive tract, there was also suspected infiltration of the sacrum, L4, Th12 vertebrae, and the junction between the frontal and parietal bones, as part of extramedullary hematopoiesis, which was not pathohistologically confirmed. Therapy with azacitidine was not initiated due to the patient's death.

Conclusion: Extramedullary hematopoiesis of the gastrointestinal tract can lead to life-threatening complications in patients with myelofibrosis, such as bleeding or ileus. In our patient, despite the use of modern therapy for the primary disease with ruxolitinib, an unfavorable outcome occurred.

Keywords: extramedullary hematopoiesis, myelofibrosis, case report

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KOLIKO JE VEROVATNA PROGRESIJA BOLESTI KOD PACIJENATA SA PRIMARNOM MIJELOFIBROZOM NISKOG RIZIKA?

HOW LIKELY IS DISEASE PROGRESSION IN PATIENTS WITH LOW-RISK PRIMARY MYELOFIBROSIS?

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SAŽETAK

Uvod: Medijana preživljavanja (OS) pacijenata sa PMF niskog rizika je preko 15 godina, ali prema „MOST” prospektivnoj studiji, progresiju bolesti ima skoro 60% ovih pacijenata.

Cilj: predstaviti tok bolesti i lečenje pacijenata sa PMF niskog rizika.

Prikaz slučaja: Svi pacijenti su imali utvrđenu PMF, IPSS niskog rizika i normalnu početnu citogenetiku. **Slučaj 1:** muškarac star 61 godinu se prezentovao maja 2016. sa Tr 772x10⁹/L, LDH 566 U/L, bez splenomegalije, JAK2V617F+. Prvobitno je lečen (2016–2020) hidroksiureom (HU), a od 2021. ruxolitinibom zbog razvoja splenomegalije i leukocitoze, uz dalju progresiju 18 meseci kasnije (slezina 26 cm, Plt 20x10⁹/L, 10% blasta u srži, složen kariotip: -5, del 7q, mar+). Uveden je Azacitidin ali zbog sepse dolazi do smrtnog ishoda, oktobra 2022. OS je 66 meseci. **Slučaj 2:** žena starosti 47 godina se prezentovala jula 2011. sa Tr 899x10⁹/L, LDH 899 U/L, slezinom 15x7cm, JAK2V617F+, ASXL+. Inicijalno je lečena sa HU, a od oktobra 2013 ruxolitinibom, zbog progresije splenomegalije (slezina 19,3 cm, LDH 1881 U/L) uz potonju normalizaciju veličine slezine, broja Tr i LDH. Pacijentkinja je u remisiji (OS 126 meseci). **Slučaj 3:** muškarac, 64 godine se prezentovao maja 2012. sa Tr 1457x10⁹/L, LDH 631 U/L, graničnom splenomegalijom, JAK2V617F-, MPL/SRSF2/U2AF1/ASXL1+. Inicijalno je lečen sa HU (maj 2012), a od aprila 2019. danazolom zbog pojave transfuzione zavisnosti. Zbog srčane insuficijencije, smrtni ishod je nastupio februara 2020. OS je 96 meseci.

Zaključak: Neki pacijenti sa PMF niskog rizika imaju progresiju bolesti i buduća istraživanja će pokazati da li rana NGS analiza non-driver mutacija i rano uvođenje terapije doprinose promeni toka bolesti.

Ključne reči: mijeloproliferativna neoplazma, primarna mijelofibroza, prognoza

ABSTRACT

Introduction: The median survival (OS) of a low-risk PMF patients is over 15 years, but according to “MOST” prospective study, nearly 60% of these patients progressed.

Objective: to present the course of disease and treatment outcome with low-risk PMF pts.

Cases report: All patients were diagnosed with PMF, had IPSS low risk and normal initial cytogenetics. **Case 1:** 61-year-old male, presented in May 2016 with Plt 772x10⁹/L, LDH 566 U/L, no splenomegaly, JAK2V617F+. He was treated with HU (2016–2020), then due to splenomegaly and leukocytosis occurrence in 2021 with ruxolitinib, but 18 mts latter disease progressed (spleen 26 cm, Plt 20x10⁹/L, 10% bone marrow blasts and complex karyotype: -5, del 7q, +mar). Azacitidin was introduced but lethal outcome occurred due to sepsis in Oct 2022. OS was 66mts. **Case 2:** 47-year-old female, presented in July 2011 with Plt 899x10⁹/L, LDH 899 U/L, spleen 15x7 cm, JAK2V617F+, ASXL+. She was initially treated with HU, but due to spleen enlargement, ruxolitinib started in Oct 2013 (spleen 19.3 cm, LDH 1881U/L), with subsequent spleen size, LDH and Plt normalization. She is still in remission (OS 126 months). **Case 3:** 64-year-old male, presented in May 2012 with Plt 1457x10⁹/L, LDH 631 U/L, borderline spleen, JAK2V617F-, MPL/SRSF2/U2AF1/ASXL1+. He was initially treated with HU and due to transfusion dependence with danazol since April 2019. Due to cardiac insufficiency lethal outcome occurred in Feb 2020 (OS 96 months).

Conclusion: Some low-risk PMF pts progress and future studies will show whether early non-driver mutations NGS analysis and early therapy onset contribute to disease course change.

Keywords: myeloproliferative neoplasm, primary myelofibrosis, prognosis

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DETECTION OF JAK2 (V617F), CALR AND MPL MUTATIONS IN PATIENTS WITH PERSISTENT THROMBOCYTOSIS

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SAŽETAK

Uvod: Mutacije JAK2, CALR i MPL gena su dobro definisani dijagnostički parametri. Svrha detekcije ovih mutacija je diferencijalna dijagnostika MPN kod bolesnika sa perzistentnom trombocitozom. JAK2 gen kodira nereceptorsku tirozin kinazu, CALR gen daje multifunkcionalni protein – kalretikulin koji je uključen u kontrolu genske aktivnosti, ćelijski rast, diferencijaciju, migraciju, ateziju i apoptozu. MPL je onkogen koji kodira receptor za trombopoetin.

Cilj: ovoga rada je detekcija najčešće prisutnih genskih mutacija, uključenih u patogenezu hroničnih mijeloproliferativnih neoplazija (MPN) sa trombocitozom.

Metode: Analizirali smo grupu od 708 pacijenata sa perzistentnom trombocitozom, ARMS-PCR metodom za detekciju JAK2 V617F mutacije. Izdvojili smo grupu od 20 pacijenata, negativnih na JAK2 mutaciju, za dalju dijagnostiku MPL W515K/L i CALR mutacija, RQ-PCR kitom za detekciju mutacija. DNK je izolovana iz periferne krvi pacijenata standardnim procedurama.

Rezultati: JAK2 V617F mutacija je bila pozitivna kod 372 bolesnika. (52,5 %). CALR mutacije su utvrđene kod 10 od 20 pacijenata (50%), najčešće Tip I (6 pacijenata, 60%) kao i Del I (6 pacijenata, 60%), Tip II (3 pacijenta, 30%), Del II (0%), Del III (3 pacijenta, 30%). Osam od deset pacijenata (80%) je imalo više od jedne mutacije. Del II mutacije nisu detektovane. W515L/K mutacije takođe nisu bile prisutne u ovoj grupi pacijenata.

Zaključak: Navedenim analizama obezbedili smo diferencijalno dijagnostičke parametre grupi bolesnika sa hroničnim mijeloproliferativnim neoplazijama. Buduća istraživanja gena uključenih u patogenezu MPN neophodna su za detekciju dijagnostičkih mutacija i utvrđivanje potencijalnih meta za molekularno ciljanu terapiju.

Cljučne reči: CALR, JAK2V617F, MPLW515K/L, MPN

ABSTRACT

Introduction: Mutations in JAK2, CALR and MPL genes, were introduced as diagnostic parameters. The aim of detecting those mutations, in the patients with persistent thrombocytosis, is to establish differential diagnose of MPN. JAK2 encodes for a non-receptor tyrosine kinase. CALR gene is coding multifunctional protein, named calreticulin, which is involved in control of gene activity, cell growth, proliferation, migration, adhesion and apoptosis. MPL is oncogene, which encodes for thrombopoietin receptor.

Objective: Detection of the most frequent gene mutations, involved in pathogenesis of myeloproliferative disorders (MPN) with thrombocytosis.

Methods: We analysed 708 patients with persistent thrombocytosis, by the ARMS-PCR method for JAK2 V617F mutation detection. We selected 20 JAK2 negative patients, for further analysis of MPL W515K/L and CALR mutations, by the RQ-PCR mutation detection kit. DNA was extracted from peripheral blood, according to standard procedures.

Results: JAK2 V617F mutation was positive in 372 patients (52.5 %). CALR mutations was detected in 10 out of 20 patients (50%), predominantly Type I (6 patients, 60%) and Del I (6 patients, 60%), Type II (3 patients, 30%), Del II (0%), Del III (3 patients, 30%). Eight of ten (80%) had more than one mutation. The Del II mutation was not detected. W515L/K mutations were not detected too, in this group of patients.

Conclusions: We provided a diagnostic parameters which differentiate a group of MPN patients with thrombocytosis. Further investigations of a new diagnostic mutations, in the genes involved in pathogenesis of MPNs, are important for defining new potential targets for molecularly targeted therapy, in treating MPNs.

Keywords: CALR, JAK2V617F, MPLW515K/L, MPN

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LATER ONSET OF TUBERCULOSIS DURING RUXOLITINIB TREATMENT IN A PATIENT WITH PRIMARY MYELOFIBROSIS

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SAŽETAK

Uvod: Ruksolitinib je značajno unapredio lečenje primarne mijelofibroze (PMF), međutim suprimira T-helper ćelije i povećava rizik od oportunističkih infekcija.

Prikaz slučaja: Septembra 2006. kod pacijentkinje uzrasta 48 godina postavljena je dijagnoza prePMF. Inicijalno: Hb 119 g/L, Le 13,3x10⁹/L, Tr 1410x10⁹/L, slezina 13,6 cm. Kultura prethodnika koštane srži: spontane BFU-E i CFU-Mk. CG uredna. Biopsija koštane srži potvrdila je dg.PMF, MF 2. Uvedena terapija Aspirin 100 mg/dn. Nakon 10g, zbog progresije splenomegalije (17,9 cm), uvedena je hidroksiurea. Uprkos eskalaciji doze, splenomegalija je napredovala. Reevaluacija maja 2023. pokazala je PMF, MF-2 i normalan kariotip. Zbog daljeg porasta slezine, avgusta 2023. uveden je ruksolitinib 2x20 mg/dn. KKS: Hb 104 g/L, Le 10,9x10⁹/L, Tr 524x10⁹/L, LDH 1013 U/L, slezina 19,5x7 cm, DIPPS intermedijarna-1-grupa. Lečenje komplikovano frekventnim transfuzijama eritrocita (hematotoksičnost), ali se slezina nakon 6 m lečenja smanjila (17,2 cm). Februara 2024. razvila je limfadenopatiju na vratu (25x11 mm) uz subfebrilnost, malaksalost i gušobolju. Marta 2024. Progresija limfnih čvorova (LN) do 6x8 cm. Biopsija je ukazala na nekrotizirajući granulom, suspekt TBC. Hospitalizovana na Klinici za infektivne bolesti, PCR-om potvrđena infekcija i započeto lečenje četverostrukom antituberkuloznom terapijom. Kultivisanjem uzoraka brisa rane na Lowenstein-Jansen podlozi detektovan MTB. CT: patološke LN na vratu desno 15x9 mm, LN hilarno desno 13x12 mm, mikronodus 6 mm u desnom vrhu pluća, slezina 150 mm. Nakon deset dana, pacijentkinja oporavljena je otpuštena. Terapija ruksolitinibom nije prekidana već redukovana za 50%.

Zaključak: Učestalost TBC kod lečenja ruksolitinibom je 1,4% od 2 do 4 meseca nakon započinjanja lečenja. Naš slučaj ukazuje na kasnu aktivaciju TBC i potrebu skrininga u slučaju nejasne febrilnosti. Redovne kontrole infektologa i hematologa su neophodne radi adekvatnog lečenja tuberkuloze bez razvoja progresije osnovne bolesti.

Ključne reči: ruksolitinib, primarna mijelofibroza, tuberkuloza, oportunističke infekcije

ABSTRACT

Introduction: Ruxolitinib has significantly improved the treatment of primary myelofibrosis (PMF), but it suppresses T-helper cells, increasing the risk of opportunistic infections.

Case report: In September 2006, 48-year-old female was diagnosed with pre-PMF. Initial findings: Hb 119 g/L, Le 13.3x10⁹/L, Tr 1410x10⁹/L, spleen 13.6 cm. Bone marrow culture showed spontaneous BFU-E and CFU-Mk. Karyotype was normal. Bone marrow biopsy confirmed PMF, MF-2. She was treated with Aspirin 100 mg/day. After 10y, due to splenomegaly progression (17.9 cm), hydroxyurea was introduced. Despite dose escalation, splenomegaly progressed. Reevaluation in May 2023 showed PMF, MF-2, and normal karyotype. Due to further spleen enlargement, ruxolitinib (2x20 mg/day) was introduced in August 2023. CBC: Hb 104 g/L, Le 10.9x10⁹/L, Tr 524x10⁹/L, LDH 1013 U/L, spleen 19.5x7 cm, DIPSS intermediate-1 risk group. She experienced frequent erythrocyte transfusions (hematotoxicity), but spleen size decreased (17.2 cm) after 6m. In February 2024, she developed cervical lymphadenopathy (25x11 mm) with fever, malaise, and sore throat. By March, lymphadenopathy progressed to 6x8 cm. Biopsy indicated necrotizing granuloma, suggestive of tuberculosis (TB). Hospitalized at Infectious Diseases Clinic, PCR confirmed TB, and quadruple antitubercular therapy was initiated. Culture on Lowenstein-Jensen medium detected MTB. CT scan-pathological cervical Ln (15x9 mm), hilar Ln (13x1 mm), a 6mm micronodule in the right lung apex, spleen 150 mm. After ten days, patient recovered and was discharged. Ruxolitinib wasn't discontinued but reduced by 50%.

Conclusion: TB incidence during ruxolitinib treatment is 1.4% within 2–4 months after initiation. Our case highlights late TB activation and need for screening in cases of unexplained fever. Regular follow-up by infectologist and hematologists is essential for managing TB without disease progression.

Keywords: ruxolitinib, primary myelofibrosis, tuberculosis, opportunistic infection

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THE INFLUENCE OF ANEMIA ON THE CLINICAL OUTCOME OF PATIENTS WITH MYELOFIBROSIS TREATED WITH RUXOLITINIB

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SAŽETAK

Uvod: Dosadašnja ispitivanja su pokazala da nova ili pogoršana anemija nije umanjila kliničku korist terapije ruksolitinibom.

Cilj: Da se analizira da li nova ili pogoršana anemija utiče na klinički ishod pacijenata sa mijelofibrozmom lečenih ruksolitinibom.

Metode: Retrospektivna analiza pacijenata lečenih tokom sedmogodišnjeg perioda. Pacijenti su podeljeni na osnovu postojanja anemije; neanemični su definisani kao Hgb ≥ 100 g/L; anemija koja zahteva transfuziju (TRA) kao Hgb < 100 g/L i primanje najmanje 2 jedinice krvi, ili anemija koja ne zahteva transfuziju (NTRA). Procenjen je ishod na osnovu odgovora slezine (SLR; smanjenje $\geq 35\%$ nakon 6 ili 12 meseci), i ukupnog preživljavanja (OS).

Rezultati: Istraživanjem je obuhvaćeno 38 pacijenata (neanemični 47,4% i anemični 52,6%). Prosečna starost pacijenata je bila 61,8 godina; 55,3% su bile žene. Bazične karakteristike su bile komparabilne između neanemičnih i anemičnih pacijenata. Nakon 6 meseci terapije, procenjeni neanemični pacijenti sa i bez nove anemije imali su stopu SLR od 33,3% naspram 44,4% ($p = 0,02$); stope su bile 45,4% naspram 44,4% ($p = 0,73$) među pacijentima sa NTRA i TRA. Nakon 12 meseci, procenjeni neanemični pacijenti sa i bez nove anemije postigli su stope SLR od 40,0% naspram 55,6% ($p = 0,09$); odgovarajuće stope su bile 25,0% naspram 33,3% ($p = 0,48$) među pacijentima sa NTRA i TRA. Slično OS je primećeno kod onih bez u poređenju sa pacijentima sa novom anemijom ($p = 0,12$). Za pacijente sa inicijalnom anemijom primećen je nešto bolji OS kod onih sa NTRA u odnosu na TRA ($p = 0,04$).

Zaključak: Rezultati ukazuju da pojava nove ili pogoršane anemije nakon iniciranja ruksolitinibom uglavnom nije smanjila kliničku korist od lečenja i podržavaju upotrebu ruksolitinibom bez obzira na inicijalnu anemiju ili razvoj anemije povezane sa lečenjem.

Ključne reči: mijelofibroza, anemija, ruksolitinib

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ABSTRACT

Introduction: Studies to date have shown that new or worsening anemia did not reduce the ruxolitinib therapy clinical benefit.

Objective: To analyze whether new or worsening anemia affects the clinical outcome of patients with myelofibrosis treated with ruxolitinib.

Methods: Retrospective analysis of patients treated over a seven-year period. Patients were divided based on anemia presence; non-anemic was defined as Hgb ≥ 100 g/L; anemia requiring transfusion (TRA) as Hgb < 100 g/L and receiving at least 2 units of blood, or anemia not requiring transfusion (NTRA). Outcome was assessed based on spleen response (SLR; reduction $\geq 35\%$ after 6 or 12 months), and overall survival (OS).

Results: Research included 38 patients (non-anemic 47.4% and anemic 52.6%). The average age was 61.8 years; 55.3% were women. Baseline characteristics were comparable between non-anemic and anemic patients. After 6 months of therapy, evaluable non-anemic patients with and without new anemia had an SLR rate of 33.3% vs. 44.4% ($p = 0.02$); rates were 45.4% vs. 44.4% ($p = 0.73$) among patients with NTRA and TRA. After 12 months, estimated non-anemic patients with and without new anemia achieved SLR rates of 40.0% vs. 55.6% ($p = 0.09$); the corresponding rates were 25.0% vs. 33.3% ($p = 0.48$) among patients with NTRA and TRA. Similar OS was observed in those without compared to patients with new anemia ($p = 0.12$). For patients with initial anemia, slightly better OS was observed in those with NTRA compared to TRA ($p = 0.04$).

Conclusion: Results indicate that occurrence of new or worsening anemia after ruxolitinib initiation generally did not reduce the treatment clinical benefit and support ruxolitinib use regardless of initial anemia or development of treatment-related anemia.

Keywords: myelofibrosis, anemia, ruxolitinib

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THE PREDICTIVE VALUE OF THE RR6 MODEL IN PATIENTS WITH MYELOFIBROSIS – A SINGLE-CENTER EXPERIENCE

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SAŽETAK

Uvod: Određeni broj bolesnika sa mijelofibrozmom lečenih ruxolitinibom tokom vremena izgubi odgovor i progredira. Prepoznavanje ranih prediktora lošeg ishoda bolesnika na terapiji ruxolitinibom ima veliki značaj.

Cilj: Utvrditi vrednosti RR6 (Response to Ruxolitinib after 6 months, eng.) modela, njegovu povezanost sa drugim pokazateljima i prediktivni značaj na ukupno preživljavanje (OS) i vreme do progresije bolesti (PFS) ispitanika.

Metode: Retrospektivno istraživanje je obuhvatilo obolele od mijelofibroze lečene ruxolitinibom najmanje 6 meseci u Kliničkom centru Vojvodine od 2017. do marta 2024. godine koji su na početku terapije imali slezinu palpabilnu za 5 i više cm ispod levog rebarnog luka.

Rezultati: Obuhvaćeno je 36 ispitanika. Prosečna vrednost OS je iznosila 32,2 meseca, a medijana PFS 26 meseci od početka terapije. RR6 je bio nizak kod 16,6%, intermedijerni i visok u po 41,7% ispitanika. Nakon 6 meseci lečenja, redukciju slezine (SR) je postiglo 30,5%, a simptomatski odgovor kod 33,3% ispitanika. Visok RR6 je bio povezan sa nepostizanjem SR (χ^2 (1, N) = 8,352, $p = 0,0154$), visokim DIPSS skorom (χ^2 (1, N) = 12,213, $p = 0,0158$), smrtnim ishodom (χ^2 (1, N) = 12,996, $p = 0,0015$) i progresijom (χ^2 (1, N) = 6,789, $p = 0,0336$). Univarijantnom analizom, RR6 je imao statistički značajan uticaj na OS (HR (95% CI) 3,7569 (1,3196–10,6962), $p = 0,0045$) i PFS ispitanika (HR (95% CI) 4,5399 (1,4408–14,3053), $p = 0,0041$).

Zaključak: RR6 model ima prediktivni značaj na ishod bolesnika sa mijelofibrozmom lečenih ruxolitinibom. On ističe važnost adekvatnog doziranja leka na postizanje SR kao i primenu dodatnih lekova u cilju ublažavanja anemije i transfuzijske zavisnosti.

Ključne reči: mijelofibroza, prognoza, ruxolitinib

ABSTRACT

Introduction: A certain number of patients with myelofibrosis treated with ruxolitinib lose response and have disease progression. Therefore, it is important to identify early predictors of inferior outcome.

Objective: To assess the value of the RR6 (Response to Ruxolitinib after 6 months) model, its correlation with other parameters, and predictive value on overall survival (OS) and progression-free survival (PFS).

Methods: We retrospectively reviewed medical records of patients with myelofibrosis with a palpable spleen of at least 5cm below the left costal margin treated with ruxolitinib for at least six months at the Clinic of Hematology, Clinical Center of Vojvodina from March 2017 to March 2024.

Results: Thirty-six patients were included. Mean OS was 32.2 months; the median PFS was 26 months. RR6 was low in 16.6%, intermediate and high in 41.7% of patients respectively. After six months, 30.5% of patients achieved spleen response (SR), and symptom response in 33.3% of patients. High RR6 was significant for failure to achieve SR (χ^2 (1, N) = 8.352, $p = 0.0154$), high DIPSS score (χ^2 (1, N) = 12.213, $p = 0.0158$), death (χ^2 (1, N) = 12.996, $p = 0.0015$) and progression (χ^2 (1, N) = 6.789, $p = 0.0336$). Univariate analysis showed a statistically significant impact of RR6 on OS (HR (95% CI) 3.7569 (1.3196–10.6962), $p = 0.0045$) and PFS of patients (HR (95% CI) 4.5399 (1.4408–14.3053), $p = 0.0041$).

Conclusion: The RR6 model predicts the outcome of myelofibrosis patients treated with ruxolitinib. It emphasizes the importance of adequate dosing of ruxolitinib and the need for additional treatment to mitigate anemia and transfusion dependency.

Keywords: myelofibrosis, prognosis, ruxolitinib

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IS TREATMENT FREE REMISSION (TFR) FEASIBLE IN CHRONIC MYELOID LEUKEMIA PATIENTS

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SAŽETAK

Uvod: Remisija bez terapije (TFR – „treatment free remission“) je jedan od savremenih ciljeva lečenja CML, međutim nije ga moguće postići kod većeg broja bolesnika. Postizanje TFR zahteva specifične biološke odlike bolesti kao i odličan, stabilan molekularni odgovor na duge staze, uz niz drugih preduslova vezanih za praćenje bolesnika (motivacija, mogućnost visokokvalitetnog PCR monitoringa).

Cilj: Analizirati mogućnost TFR kod bolesnika lečenih na Klinici za hematologiju UKCS.

Metode. U grupi od 330 bolesnika kod 13 bolesnika je pokušana TFR procedura uz praćenje genetskih nalaza u skladu sa našim mogućnostima „real time“ PCR testom.

Rezultati: Od 13 bolesnika 7 je bilo na imatinibu, 3 na nilotinibu a 3 bolesnika su lečena nilotinibom kroz ENEST Path studiju. Razlozi za TFR su bili želja bolesnika (6) odnosno studija (3), trudnoća (3) dok je kod jedne bolesnice (na nilotinibu) razlog bio vaskularni problemi. Dužina prethodne TKI terapije je bila prosečno 135 meseci (68–190), a kod 10 bolesnika dokumentovana dužina MR4 je bila > 24 meseca (prosečno 50 meseci). U celini, 9 bolesnika (69%) je ostalo u remisiji bez terapije (MR > 3) sa prosečnom dužinom TFR od 62 meseca (13–132 meseca). Četiri bolesnika su izgubila TFR u periodu do 4 meseca od prekida i nastavila su terapiju (2 bolesnika nilotinib, 1 bolesnica imatinib i trudnica PEG-IFN) sa ponovo dobrim PCR odgovorom. Do sada su rođene dve zdrave bebe.

Zaključak: Naše iskustvo pokazuje da je u selektovanim slučajevima i posebnim situacijama (trudnoća) primena TFR pristupa u lečenju CML izvodljiva i uspešna, ali zahteva poseban pristup za svakog pojedinačnog bolesnika.

Cljučne reči: hronična mijelodna leukemija, remisija bez terapije, prekid lečenja, PCR monitoring

ABSTRACT

Introduction: Treatment free remission (TFR) is one of new, powerful goals of CML treatment, but is seldom achieved in most of patients, TFR achievement requires specific biological features of leukemia, excellent, stable molecular response and other prerequisite conditions concerning patient's follow-up like motivation and high quality PCR monitoring,

Objective: To evaluate possibility of TRF in patients with CML followed on Clinic of Hematology UKCS

Methods: Among 330 patients, TFR was attempted with “real time” PCR monitoring according to our abilities.

Results: From 13 patients, 7 patients were on imatinib, 3 patients were on nilotinib, 3 patients were enrolled in nilotinib based ENEST Path clinical trial. Reasons for TFR were patients wish (6) or trial (3), pregnancy (3) and in one patient (on nilotinib) TFR was due to vascular problems. Length of previous TKI therapy was 135 months (68–190), and in 10 patients documented length of MR4 was > 24 months (average 50 months). In general, 9 patients (69%) remained in TFR (MR > 3) with average length of 62 months (13–132 months). Four patients lost TFR within 4 months since TKI stop, and commenced same treatment (two nilotinib, one imatinib and pregnant patient PEG-IFN) with achievement of good PCR response. Two healthy babies were delivered so far.

Conclusion: Our experience shown that in selected and/or special cases (pregnancy) TFR approach in CML treatment is feasible and successful but with special attention to each patient's features.

Keywords: chronic myeloid leukemia, treatment free remission, treatment stop, PCR monitoring

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SUCCESSFULNESS OF SECOND LINE TREATMENT WITH NILOTINIB IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA – SINGLE CENTER EXPERIENCE

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SAŽETAK

Uvod: Nakon 5 godina terapije prve linije imatinibom (inhibitor tirozin-kinaze-TKI) oko 50% pacijenata sa hroničnom mijeloidnom leukemijom, gube terapijski odgovor i/ili progrediraju. Zbog toga, približno 40% – 60% bolesnika mora da pređe na druge TKI. Pravilni odabir lekova druge linije u ovoj visoko rizičnoj populaciji je zbog toga od primarnog značaja za poboljšanje ukupnog ishoda lečenja.

Cilj: Cilj ovog rada je bio analiza molekularnog odgovora na nilotinib kao drugu liniju lečenja pacijenata sa hroničnom mijeloidnom leukemijom.

Metode: Ova retrospektivna studija je obuhvatila ukupno 31 pacijenta obolelih od hronične mijeloidne leukemije aktuelno na terapiji nilotinibom kao drugom linijom lečenja. Podaci su prikupljeni iz elektronske baze podataka pacijenata, a za statističku analizu je korišćen SPSS 15.0 program. Studija je rađena u skladu sa principima Helsinške deklaracije.

Rezultati: Duboki molekularni odgovor zabeležen je kod 16 pacijenata (62,5%) na nilotinibu, dok je veliki molekularni odgovor postignut kod sedmoro pacijenata (22,58%). Kod sedmoro pacijenata (22,58%) je došlo do gubitka molekularnog odgovora, ali su ovi pacijenti prijavili neredovno uzimanje leka. Terapija nilotinibom je prekinuta kod samo jednog pacijenta usled toksičnosti. Prosečno vreme terapije nilotinibom bilo je 62,39 meseci.

Zaključak: U ovoj studiji sa podacima iz realnog života, je pokazana efikasnost Nilotinib-a u smislu postizanja i održavanja dubokog ili velikog molekularnog odgovora u drugoj liniji lečenja bolesnika sa hroničnom mijeloidnom leukemijom.

Ključne reči: hronična mijeloidna leukemija, inhibitori tirozin kinaze, nilotinib

ABSTRACT

Introduction: Up to 50% of patients with chronic myeloid leukemia, who initiate first-line tyrosine kinase inhibitor (TKI) therapy with imatinib, experience loss of response or disease progression, after 5 years of frontline therapy. Approximately, about 40% – 60% of patients have to pass on alternative TKIs. The choice of adequate second line TKI inhibitor is of utmost importance to improve overall outcome of these high-risk patients.

Objective: The aim of this study was to evaluate the molecular response to nilotinib as a second line treatment for patients with chronic myeloid leukemia in the real-life setting.

Methods: This retrospective study included 31 chronic myeloid leukemia patients receiving Nilotinib as second-line treatment. Data was collected from the patients' medical records and the statistical analysis was performed using the SPSS 15.0 program. The study was conducted in accordance with the Declaration of Helsinki.

Results: Deep molecular response was recorded in 16 patients (62.5%) receiving nilotinib, whereas major molecular response was achieved in seven patients (22.58%). Seven patients (22.58%) had a loss of molecular response, however, these patients reported irregular use of the medication. Nilotinib was discontinued in just one patient due to toxicity. Average time of nilotinib treatment in patients was 62.39 months.

Conclusion: This real-life study has shown Nilotinib to be efficient in achievement and maintaining deep or major molecular response in second-line treatment of chronic myeloid leukemia.

Keywords: chronic myeloid leukemia, tyrosine kinase inhibitors, nilotinib

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TRANSPLANTACIJA MATIČNIH ĆELIJA HEMATOPOEZE

HEMATOPOIETIC STEM CELL TRANSPLANTATION

WEST NILE VIRUS NEUROINVASIVE DISEASE FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM-CELL TRANSPLANTATION – A CASE REPORT

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SAŽETAK

Uvod: Virus Zapadnog Nila (VZN) najčešće se prenosi ubodom zaraženog komarca. Opisani su i slučajevi prenosa produktima krvi ili putem transplantiranih organa. U 80% slučajeva infekcija prolazi asimptomatski. Kod < 1% javlja se teška, neuroin vazivna forma bolesti.

Cilj: Prikazati slučaj infekcije VZN nakon transplantacije matičnih ćelija hematopoeze.

Metode: U dijagnostici infekcije korištene su serološke metode i PCR.

Rezultati: Bolesnici starosti 31 godinu postavljena je dijagnoza rane prekursorke T-ćelijske akutne limfoblastne leukemije. Nakon indukcije i konsolidacije prema CALGB 10403 protokolu, te kondicionog TBF režima uz antitumocitni globulin, bolesnica je primila transplantat matičnih ćelija hematopoeze od HLA identične rođene sestre. Do engraftmenta granulocita dolazi +12. dana od transplantacije. Narednog dana kod bolesnice se javlja raš, a +14. dana i tremor ruku, blaga psihička izmenjenost, promene u ponašanju i visoka febrilnost. Markeri inflamacije su bili u referentnom opsegu. Konsultovani su infektolog i neurolog, te je sprovedena dodatna dijagnostika. Kompjuterizovanom tomografijom i magnetnorezonantnim pregledima nisu viđeni znaci akutnog neurološkog oboljenja. U likvoru nije dokazano prisustvo VZN, kao ni drugih virusnih i bakterijskih uzročnika ili malignih ćelija (lumbalna punkcija rađena 6. dana bolesti). IgM antitela u krvi na VZN su bila pozitivna. Postavljena je dijagnoza neuroin vazivne forme infekcije VZN. Kako ne postoji kauzalna terapija, lečenje je sprovedeno primenom intravenskih imunoglobulina, po 10g tokom pet dana, uz sistemsku kortikosteroidnu terapiju, nakon čega dolazi do smirivanja febrilnosti i poboljšanja opšteg stanja.

Zaključak: Transplantirani bolesnici, kao imunokompromitovani, a često i politransfundovani, naročito su podložni razvoju simptomatske bolesti u slučaju izloženosti VZN.

Ključne reči: Zapadni Nil, virus, encefalitis, transplantacija matičnih ćelija

ABSTRACT

Introduction: Typically, the West Nile virus (WNV) is transmitted through the bite of an infected mosquito. It may also be disseminated by infected blood products or transplanted organs. In 80% of cases, the infection remains asymptomatic. Less than 1% of patients will develop a severe, neuroinvasive form of the disease.

Objective: To present a case of WNV infection after hematopoietic stem cell transplantation (HSCT).

Methods: Serological methods and PCR were used to establish the diagnosis.

Results: A 31-year-old female with early precursor T-cell acute lymphoblastic leukemia received HSCT from an HLA-identical sibling after induction and consolidation therapy with CALGB 10403, followed by TBF conditioning and anti-thymocyte globulin. Neutrophil engraftment occurred 12 days post-transplant. One day later, the patient developed a skin rash, followed by hand tremors, slight psychological alterations, changes in behavior, and high fever (+14 day), without laboratory signs of inflammation. An infectious disease specialist and a neurologist were consulted, so further diagnostic tests were conducted. Computed tomography and magnetic resonance imaging scans showed no signs of acute neurological disease. A lumbar puncture on day 6 of the illness revealed no pathogens or malignant cells in the cerebrospinal fluid. Serum testing identified WNV IgM antibodies. A neuroinvasive WNV infection was diagnosed. Since there is no specific therapy available, the patient was treated with intravenous immunoglobulins (10 grams daily for five days) and systemic corticosteroids. Following treatment, her fever decreased, and her overall health improved.

Conclusion: HSCT patients are particularly vulnerable to symptomatic WNV infection due to their immunocompromised status and frequent blood transfusions.

Keywords: West Nile, virus, encephalitis, stem-cell transplantation

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EARLY COMPLICATIONS FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM-CELL TRANSPLANTATION – OUR EXPERIENCE

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SAŽETAK

Uvod: Transplantacija matičnih ćelija hematopoeze (TMČH) je za mnoge hematološke bolesti jedina terapija koja potencijalno dovodi do izlječenja, ali sa sobom nosi i brojne rizike.

Cilj: Utvrditi tip i učestalost ranih komplikacija (unutar 100 dana) nakon alogene TMČH.

Metode: Retrospektivno je analizirano 28 bolesnika kod kojih je urađeno 30 alogenih TMČH (17 srodnih i 13 nesrodnih) na Klinici za hematologiju Univerzitetskog Kliničkog centra Vojvodine, u periodu od februara 2017. do juna 2024. godine. Podaci su dobijeni uvidom u medicinsku dokumentaciju i obrađeni standardnim metodama deskriptivne statistike.

Rezultati: Medijana starosti bolesnika je iznosila 38 godina (raspon 19–66). Broj muškaraca i žena je bio podjednak. Akutna leukemija je bila najčešća indikacija (15 bolesnika sa mijeloblastnom i 8 sa limfoblastnom leukemijom). U vreme transplantacije osnovna bolest je bila u stanju kompletne remisije kod 20 bolesnika (66% bolesnika). Infektivne komplikacije zabeležene su u ranom posttransplantacionom periodu u 93% slučajeva – najčešće bakterijske (60% svih infekcija). Reaktivaciju citomegalovirusa imalo je 25% bolesnika. Jedna trećina imala je neku manifestaciju akutne bolesti kalema protiv domaćina, najčešće blaži kožni ili gornji gastrointestinalni oblik. Teška gastrointestinalna forma bolesti je zabeležena kod jednog bolesnika, dok je jedan imao zahvatanje kože gradus 4. Trombozne komplikacije, najčešće u venskom sistemu, imalo je 13% bolesnika, a kod jednog je zabeležena trombozna mikroangiopatija. Jedan bolesnik je imao venookluzivnu bolest. Smrtnost unutar prvih 100 dana je bila 20%.

Zaključak: Uprkos visokom riziku same procedure i brojnim komplikacijama, alogena TMČH ostaje terapija izbora i potencijalno jedina šansa za izlječenje za mnoge obolele od najagresivnijih hematoloških bolesti.

Ključne reči: transplantacija matičnih ćelija, alogena, komplikacije

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ABSTRACT

Introduction: For many hematological diseases hematopoietic stem-cell transplantation (HSCT) is the only therapy potentially leading to cure. However, it carries numerous risks.

Objective: To determine the type and frequency of early complications (within the first 100 days) following allogeneic HSCT.

Methods: Medical records were reviewed and retrospectively analyzed to obtain data on 28 patients who underwent 30 allogeneic HSCTs (17 related and 13 unrelated) at the Hematology Clinic, University Clinical Center of Vojvodina, from February 2017 through June 2024. Data were analyzed using standard descriptive statistical procedures.

Results: The median age was 38 (range 19–66). Men and women were equally represented. The most frequent indication for HSCT was acute leukemia (15 individuals with myeloblastic and 8 with lymphoblastic leukemia). The underlying disease was in complete remission in 20 patients (66%) at the time of HSCT. Infectious complications were noted in 93% of patients during the early post-transplant period. Bacterial infections were the most common (60%). CMV reactivation occurred in 25%. Thirty percent of patients exhibited mild acute graft-versus-host disease. Typically, skin or upper gastrointestinal tract were involved. One patient experienced severe gastrointestinal form, while another suffered skin involvement grade 4. Thrombotic complications, mostly venous, were found in 13% of patients, including one case of thrombotic microangiopathy. One patient exhibited veno-occlusive disease. Mortality throughout the first 100 days reached 20%.

Conclusion: Despite the high risk of the procedure and numerous complications, allogeneic HSCT remains the standard of care and may be the only curative therapy for many patients facing the most aggressive hematological disorders.

Keywords: stem cell transplantation, allogeneic, complications

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ANALIZA EFEKTIVNOSTI LETERMOVIRA KAO PRIMARNE PROFILAKSE CMV REAKTIVACIJE NAKON ALOGENE TRANSPLANTACIJE MATIČNIH ČELIJA HEMATOPOEZE: STUDIJA JEDNOG CENTRA

ANALYSIS OF LETERMOVIR'S EFFECTIVENESS AS PRIMARY PROPHYLAXIS AGAINST CMV REACTIVATION FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANT: A SINGLE-CENTER STUDY

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SAŽETAK

Uvod: CMV reaktivacija predstavlja značajan problem nakon alogene transplantacije matičnih ćelija hematopojeze (allo-TMČH) utičući na funkciju grafta i bolest kalema protiv domaćina (GvHD). Letermovir je uveden sa ciljem redukcije stope reaktivacije CMV i poboljšanja post-transplantacionih ishoda.

Cilj: Cilj je evaluacija efektivnosti letermovira kao CMV profilakse nakon allo-TMČH, fokusirajući se na ranu (pre d+100) i kasnu (nakon d+100) CMV reaktivaciju i uticaj na funkciju grafta i GvHD.

Metode: Retrospektivno smo analizirali 136 pacijenata podvrgnutih allo-TMČH od decembra 2017. CMV-seropozitivni recipijenti su primili letermovir (240 mg/dan). Replikacija CMV praćena je inicijalno nedeljno, dvonedeljno do d+100 i potom mesečno. Letermovir je primenjivan do d+100 ili do CMV reaktivacije, definisane kao konsekutivni porast virusnih kopija tokom 7 dana isključujući blip. U slučaju reaktivacije primenjivana je preemptivna terapija osim ukoliko je potvrđen blip.

Rezultati: Većina pacijenata (prosečne starosti $39,8 \pm 12,3$ godina) primila je mijeloablativno kondicioniranje (69,1%). Donori su bili MUD (41,9%), MMUD (14,0%), MRD (33,8%) i haploidentični (10,3%). Distribucija CMV-serostatusa je bila R+/D+ kod 75 (55,1%), R-/D+ kod 11 (8,1%), R+/D- kod 46 (33,8%) i R-/D- kod 4 (2,9%) pacijenta. Rana CMV reaktivacija registrovana kod 65 pacijenata (47,8%), značajno manje (13,8%) u letermovir grupi ($p = 0,000$). Kasna CMV reaktivacija zabeležena kod 43,6% primalaca letermovira. Primarna slabost kalema (PGF) uočena kod 25,7%, pri čemu je 80,0% slučajeva bilo povezano sa ranom CMV reaktivacijom. Rana reaktivacija korelirala je sa pojavom hepatičnog aGvHD (5,1%), a kasna reaktivacija sa hroničnim GvHD (23,5%).

Zaključak: Letermovir je efikasno redukovao ranu CMV reaktivaciju ali nije pokazao značajan uticaj na kasnu reaktivaciju što ukazuje na potrebu za produženom profilaksom nakon d+100.

Cljučne reči: allo-TMČH, CMV, letermovir, profilaksa

ABSTRACT

Introduction: CMV reactivation is a significant concern post-allogeneic hematopoietic stem cell transplant (allo-HSCT), impacting graft function and correlating with graft-versus-host disease (GvHD). Letermovir has been adopted to reduce CMV reactivation rates and improve post-transplant outcomes.

Objective: Study aimed to evaluate letermovir's effectiveness as CMV prophylaxis in allo-HSCT recipients, focusing on early (before day+100) and late (after day+100) CMV reactivation, and its impact on graft function and GvHD.

Methods: We retrospectively analyzed 136 allo-HSCT recipients treated since December 2017. CMV-seropositive recipients received letermovir (240 mg/day). CMV DNAemia was monitored weekly initially, then bi-weekly until day+100, and monthly thereafter. Letermovir was continued until day+100 or CMV reactivation, defined as consecutive viral copy increases over 7 days, excluding blips. Upon reactivation, preemptive therapy was initiated unless a blip was confirmed.

Results: Patients (mean age 39.8 ± 12.3 years) predominantly received myeloablative conditioning (69.1%). Donors included MUD (41.9%), MMUD (14.0%), MRD (33.8%), and haploidentical (10.3%). The distribution of CMV serostatus was: R+/D+ in 75 (55.1%), R-/D+ in 11 (8.1%), R+/D- in 46 (33.8%) and R-/D- in 4 (2.9%) patients. Early CMV reactivation occurred in 65 patients (47.8%), significantly less (13.8%) in letermovir group ($p = 0.000$). Late CMV reactivation affected 43.6% of letermovir recipients. Primary graft failure (PGF) was seen in 25.7%, with 80.0% of PGF cases associated with early CMV reactivation. Early CMV reactivation correlated with acute hepatic GvHD (5.1%), while late reactivation correlated with chronic GvHD (23.5%).

Conclusion: Letermovir effectively reduced early CMV reactivation but showed no significant impact on late reactivation, suggesting potential necessity of extended prophylaxis post day+100.

Keywords: allo-HSCT, CMV, letermovir, prophylaxis

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EXTRACORPORAL PHOTOPHERESIS IN CHILDREN - SINGLE CENTER EXPERIENCE

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SAŽETAK

Uvod: Ekstrakorporalna fotofereza (EF) je imunomodulatorna terapija tokom koje se postupkom afereze iz periferne krvi izdvajaju autologne mononuklearne ćelije (MNC), ex vivo im se dodaje 8-metoksipsoralen, ćelije se zrače UVA zracima a zatim reinfunduju pacijentu. Uspešno se primenjuje u terapiji kortikosteroid rezistentne akutne i hronične bolesti kalem protiv domaćina (engl. graft versus host disease GVHD) nakon alogene transplantacije matičnih ćelija hematopoeze.

Cij: Prikaz karakteristika afereznih procedura i kvaliteta produkta MNC za EF kod dvoje dece sa akutnim i hroničnim GVHD-om.

Metode: Procedure su sprovedene u periodu od jula 2023. do jula 2024. godine na afereznom sistemu Spectra Optia. Za antikoagulaciju je korišćen rastvor Acid Citrate Dextrose-A (ACD-A). Hipokalcemija je prevenirana davanjem tableta kalcijum karbonata. Za UVA ozračivanje je korišćen MacoGenic iluminator, offline metoda.

Rezultati: Ukupno je sprovedeno 45 afereznih procedura kolekcije MNC za EF kod dva pacijenta muškog pola uzrasta 9 i 10 godina. Prvi pacijent DJ je ispoljio simptome GVHD-a na koži i očima, a drugi, FD, na crevima. Afereze MNC su prosečno trajale $127,7 \pm 32,1$ minut, sa prosečnom brzinom utoka $30 \pm 0,01$ ml/min. Prosečno je procesiran 1 cirkulatorni volumen krvi, odnos krvi i antikoagulansa bio je $10,6 \pm 1,3$ i upotrebjeno je $270,3 \pm 57,3$ ml ACD-A. Aferezom je prosečno prikupljeno $85,6 \pm 14,7\%$ MNC, što je u proseku $18,1 \pm 2,95 \times 10^8$ u $38,5 \pm 7,7$ ml produkta, hematokrita $1,8 \pm 0,99\%$. Srednja vrednost jonizovanog kalcijuma pre/posle afereze bila je $1,07 \pm 0,04 / 1,01 \pm 0,03$ mmol/L. Kod pacijenata je zapaženo kliničko poboljšanje nakon dva meseca terapije EF-om.

Zaključak: Afereza MNC za EF je bezbedna i efikasna procedura kod dece sa GVHD-om.

Ključne reči: ekstrakorporalna fotofereza, GVHD, deca, mononuklearne ćelije, afereza

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ABSTRACT

Introduction: Extracorporeal photopheresis (ECP) is an immunomodulatory therapy during which autologous mononuclear cells (MNC) are collected from peripheral blood by apheresis, 8-methoxy psoralen is added to them ex vivo, the cells are irradiated with UVA rays, and then reinfuse into the patient. It successfully treats acute and chronic corticosteroid-resistant graft-versus-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation.

Objective: Presentation of apheresis procedures characteristics and MNC product quality for ECP in two children with acute and chronic GVHD.

Methods: The procedures were carried out on the Spectra Optia apheresis system from July 2023 to July 2024. Acid Citrate Dextrose A (ACD-A) solution was used for anticoagulation. Hypocalcemia was prevented by giving calcium carbonate tablets. MacoGenic illuminator, an offline method, was used for UVA irradiation.

Results: 45 apheresis procedures of MNC collection for ECP were performed in two male patients aged 9 and 10 years. The first patient, DJ, showed symptoms of GVHD on the skin and eyes, and the second, FD, on the intestines. The apheresis of MNC lasted $127,7 \pm 32,1$ minute, with an average inlet flow rate of $30 \pm 0,01$ ml/min. On average, one total blood volume was processed, with an ACD-A ratio $10,6 \pm 1,3$, and $270,3 \pm 57,3$ ml of ACD-A used. An average of $85,6 \pm 14,7\%$ of MNC was collected, which is $18,1 \pm 2,95 \times 10^8$ in $38,5 \pm 7,7$ ml of product with hematocrit $1,8 \pm 0,99\%$. The mean value of ionized calcium before/after apheresis was $1,07 \pm 0,04 / 1,01 \pm 0,03$ mmol/L. Clinical improvement was observed in patients after two months of ECP therapy.

Conclusion: Apheresis of MNC for ECP is safe and effective procedure in children with GVHD.

Keywords: extracorporeal photopheresis, GVHD, children, mononuclear cells, apheresis

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THE APPLICATION OF EXTRACORPORAL PHOTOPHERESIS IN THE TREATMENT OF “GRAFT VERSUS HOST DISEASE”

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SAŽETAK

Uvod: Bolest „graft-versus-host“ (GvHD) je ozbiljna komplikacija i glavni uzrok mortaliteta i morbiditeta nakon alogene transplantacije matičnih ćelija hematopoeze (MČH). Deli se na akutni (aGvHD) i hronični (cGvHD) oblik. Kod 50% pacijenata se može javiti aGvHD (14% sa teškim oblikom) sa smrtnošću od 36%. Hronični GvHD ostaje preovlađujući uzrok mortaliteta bez recidiva (NRM) kod pacijenata koji prežive duže od dve godine nakon transplantacije, negativno utičući na kvalitet života i na dugoročne ishode. Može da izazove oštećenja tkiva usled fibroze i dovede pacijente u visok rizik od smrti zbog infekcija.

Cilj: Primeniti modalitet lečenja – ekstrakorporalnu fotoferezu (ECP), tokom koje se mononuklearne ćelije izlažu ultraljubičastom A zračenju u prisustvu fotosenzibilizujućeg agensa (8-MOP), i utvrditi efikasnost u lečenju GvHD.

Metode: Počev od 12. oktobra 2023. godine, na Institutu za transfuziologiju i hemobiologiju VMA se primenjuje procedura ekstrakorporalne fotofereze, korišćenjem „offline“ aparata „Macogenic G2“ i fotosenzitišućeg agensa 8-MOP-a.

Rezultati: Ukupno je izvedeno 40 procedura, 8 kod pacijenta sa aGvHD i 32 kod pacijentkinja sa cGvHD. Kod pacijenta sa aGvHD je u početku rađena procedura svaka tri dana, da bi kasnije fotofereza rađena nakon četiri, odnosno nakon 12–16 dana. Prosečno je prikupljeno od 120–130 ml ćelija sa 30 ml plazme. Kod pacijentkinja sa cGvHD je urađeno 32 procedure sa vremenskim razmakom od šest do 15 dana, a prikupljeno je u proseku oko 120 ml ćelija uz 30 ml plazme.

Zaključak: Tokom primene ECP, nisu zabeležene nikakve nuspojave kod pacijenata, a efekti su bili veoma značajni i ohrabrujući u lečenju GvHD nakon transplantacije MČH.

Ključne reči: transplantacija, ekstrakorporalna fotofereza, GvHD

ABSTRACT

Introduction: Graft-versus-host disease (GvHD) is a serious complication and the main cause of mortality and morbidity after allogeneic hematopoietic stem cell transplantation (HSCT). Acute (aGvHD) may develop 50% of patients with a mortality rate of 36%. Chronic GvHD remains the predominant cause of non-relapse mortality (NRM) in patients surviving beyond two years post-transplantation. It can cause tissue damage due to fibrosis and put patients at high risk of death from infections.

Objective: To apply the treatment modality - extracorporeal photopheresis (ECP), during which mononuclear cells are exposed to ultraviolet A radiation in the presence of a photosensitizing agent (8-MOP), and to determine the effectiveness in the treatment of GvHD.

Methods: At the Institute of Transfusion and Hemobiology, ECP is applied on October 12, 2023, using the “offline” apparatus “Macogenic G2” and 8-MOP.

Results: A total of 40 procedures were performed, eight in patients with aGvHD and 32 in patients with cGvHD. In the patient with aGvHD, the procedure was initially performed every three days, and later photopheresis was performed after four, that is, after 12–16 days. An average of 120–130 mL of cells with 30 mL of plasma was collected. In patients with cGvHD, 32 procedures were performed with a time interval of six to 15 days, and an average of about 120 mL of cells and 30 mL of plasma were collected.

Conclusion: During the administration of ECP, no side effects were noted, and the effects were very significant and encouraging in the treatment of GvHD after HSCT.

Keywords: transplantation, extracorporeal photopheresis, GvHD

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ASSOCIATION OF IMMUNE RECONSTITUTION WITH EARLY
AND LATE CMV REACTIVATION FOLLOWING ALLOGENEIC
HEMATOPOIETIC STEM CELL TRANSPLANTATION

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SAŽETAK

Uvod: Imunska rekonstitucija subpopulacija ćelija urođene i stečene imunosti nakon alogene transplantacije je dinamičan proces. Utvrđeno je da vrednosti limfocitnih subpopulacija mogu imati uticaja na citomegalovirusnu (CMV) reaktivaciju, stopu relapsa, bolest kalema protiv domaćina, kao i preživljavanje nakon transplantacije.

Cilj rada: Ispitati povezanost vrednosti apsolutnog broja B-limfocita, CD4+ T-limfocita (CD4+T-Li), CD8+ T-limfocita (CD8+T-Li), NK ćelija i NKT ćelija sa učestalošću rane i kasne CMV reaktivacije.

Metode: Analizirani su podaci 97 pacijenata kod kojih je sprovedena alogena transplantacija na Klinici za hematologiju UKCS u periodu 2017-2024. Vrednost subpopulacija limfocita određivana je na d+30, d+90, d+180 i d+360 i analizirana je njihova povezanost sa ranom i kasnom CMV reaktivacijom. Rana reaktivacija je definisana kao pozitivan PCRquant (> 100 kopija/ml krvi) do d+100 nakon transplantacije, a kasna je detektovana kao replikacija nakon d+100. U statističkoj obradi korišćen je Mann-Whitney U test.

Rezultati: Kod pacijenata sa ranom CMV reaktivacijom, broj CD8+ T-Li na d+90 je bio statistički značajno veći (medijana 83/uL vs. 32/uL, $p = 0,03$). Takođe, kod ovih pacijenata postoji trend većeg broja NK ćelija na d+90 ($p = 0,08$). Kod pacijenata sa kasnom CMV reaktivacijom, broj CD8+ T-Li na d+360 je bio značajno veći (medijana 230/uL vs. 119/uL, $p < 0,001$), dok je broj CD4+ T-Li na d+30 i d+90 bio manji (medijana 7/uL vs. 23,5/uL, $p = 0,02$, i 47/uL vs. 60/uL, $p = 0,03$). Takođe, kod ovih pacijenata broj NKT ćelija na d+30 bio je manji (medijana 18/uL vs. 31/uL, $p = 0,03$).

Zaključak: Posttransplantacione vrednosti različitih subpopulacija limfocita odraz su specifičnog antivirusnog odgovora i imaju značaj u prepoznavanju pacijenata sa povećanim rizikom od CMV reaktivacije.

Ključne reči: imunska rekonstitucija, alogena transplantacija, CMV reaktivacija

ABSTRACT

Introduction: Immune reconstitution of innate and acquired immunity following allogeneic haematopoietic stem cell transplantation (HSCT) is a dynamic process. It is known that lymphocyte subpopulation values can affect survival and impact the incidence of CMV reactivation, relapse and graft versus host disease.

Objective: To investigate the association between absolute counts of B lymphocytes, CD4+ T lymphocytes, CD8+ T lymphocytes, NK cells, NKT cells, and the incidence of early and late CMV reactivation post HSCT.

Methods: Ninety-seven patients undergoing allogeneic HSCT at the Clinic of Hematology, University Clinical Center of Serbia from 2017 to 2024 were analyzed. Lymphocyte subpopulations were quantified at days +30, +90, +180, and +360 post-transplantation. Statistical analysis employed the Mann-Whitney U test to evaluate associations between lymphocyte subpopulation counts and early (within 100 days) and late (after day 100) CMV reactivation (PCRquant > 100 copies/ml).

Results: Patients experiencing early CMV reactivation exhibited significantly higher CD8+ T- lymphocytes counts at day +90 (median 83/uL vs. 32/uL, $p = 0,03$) and a trend towards elevated NK cell counts at day +90 ($p = 0,08$). Those with late CMV reactivation demonstrated significantly higher CD8+ T-lymphocytes counts at day +360 (median 230/uL vs. 119/uL, $p < 0,001$) and lower CD4+ T-lymphocyte counts at days +30 and +90 (median 7/uL vs. 23.5/uL, $p = 0,02$ and 47/uL vs. 60/uL, $p = 0,03$, respectively). Additionally, NKT cell counts were lower at day +30 in patients with late CMV reactivation (median 18/uL vs. 31/uL, $p = 0,03$).

Conclusion: Quantitative assessment of lymphocyte subpopulations post HSCT reflects specific antiviral response and aids in identifying patients at heightened risk of CMV reactivation.

Keywords: immune reconstitution, allogeneic transplantation, CMV reactivation

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IMPACT OF PRETRANSPLANTATION FACTORS ON IMMUNE RECONSTITUTION FOLLOWING ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION

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SAŽETAK

Uvod: Imunska rekonstitucija se definiše oporavkom subpopulacija limfocita nakon alogene transplantacije. Usporena rekonstitucija predstavlja veliki klinički izazov i rezultuje visokim stopama posttransplantacionih komplikacija, uključujući infekciju i relaps bolesti.

Cilj: Ispitati uticaj različitih pretransplantacionih faktora na apsolutne vrednosti subpopulacija limfocita u posttransplantacionom toku.

Metode: Analizirani su podaci 97 pacijenata kod kojih je sprovedena alogena transplantacija na Klinici za hematologiju UKCS 2017.-2024. Analiziran je uticaj pola recipijenta i donora, starosti recipijenta, broja CD34+ ćelija u transplantatu, jačine kondicionog režima (MAC-eng. myeloablative conditioning i RIC-eng. reduced intensity conditioning), CMV serostatusa recipijenta (IgG negativan i IgG pozitivan) i tipa alogene transplantacije (srodna, eng. matched related donor-MRD i nesrodna-eng. matched unrelated donor-MUD) na imunsku rekonstituciju. Vrednosti subpopulacija limfocita (CD4+, CD8+, B-limfocita, NK i NKT ćelija) određivane su na d+30, d+90, d+180 i d+360. U statističkoj obradi korišćen je Spearman-ov test korelacije i Mann-Whitney U test.

Rezultati: U grupi pacijenata sa MRD vs. MUD transplantacijom uočena je značajno veća vrednost B i CD4+ limfocita na d+30 ($p = 0,005$ i $p < 0,001$, respektivno), CD4 limfocita na d+90 ($p = 0,017$), CD8+ limfocita na d+30 ($p < 0,001$), d+90 ($p < 0,001$), NKT limfocita na d+30 ($p = 0,01$), d+90 ($p < 0,001$), d+180 ($p < 0,001$) i d+360 ($p = 0,017$) u MRD grupi. U grupi CMV IgG- pacijenata uočena je značajno veća vrednost B-limfocita na d+30 ($p = 0,029$) kao i vrednost CD4+ limfocita na d+90 ($p = 0,022$) i d+180 ($p = 0,032$). Pol i starost recipijenta, pol donora, broj CD34+ ćelija i jačina kondicionog režima nisu uticali na dinamiku imunske rekonstitucije.

Zaključak: Pacijenti kod kojih je sprovedena MRD transplantacija imaju bržu dinamiku imunske rekonstitucije, pre svega u prvih šest meseci.

Ključne reči: imunska rekonstitucija, alogena transplantacija, pretransplantacioni faktori

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ABSTRACT

Introduction: Immune reconstitution after allogeneic hematopoietic stem cell transplantation (HSCT) involves the recovery of lymphocyte subpopulations. Delayed immune recovery presents a significant clinical challenge and correlates with increased rates of post-transplant complications, including infections and relapse.

Objective: To explore how various pretransplantation factors influence lymphocyte subpopulation counts post-HSCT.

Methods: Ninety-seven patients who underwent allogeneic HSCT at the Clinic for Hematology between 2017 and 2024 were analyzed. Lymphocyte subpopulations (CD4+, CD8+, B lymphocytes, NK cells, and NKT cells) were assessed at days +30, +90, +180, and +360 post-transplantation. Factors examined included recipient and donor sex, recipient age, CD34+ cells in product, conditioning regimen intensity (myeloablative vs. reduced intensity), recipient CMV serostatus (IgG- vs. IgG+), and type of allogeneic transplantation (matched related donor-MRD vs. matched unrelated donor-MUD). Statistical analysis involved Spearman's rank-correlation test and Mann-Whitney U test.

Results: MRD transplantation was associated with significantly higher counts of B and T lymphocytes at day +30 ($p = 0.005$ and $p < 0.001$, respectively), CD4+ T lymphocytes at days +90 ($p = 0.017$), CD8+ T lymphocytes at days +30 ($p < 0.001$) and +90 ($p < 0.001$), and NKT cells at days +30 ($p = 0.01$), +90 ($p < 0.001$), +180 ($p < 0.001$), and +360 ($p = 0.017$). CMV IgG negative patients also showed significantly higher counts of B lymphocytes at day +30 ($p = 0.029$), CD4+ T lymphocytes at days +90 ($p = 0.022$) and +180 ($p = 0.032$). Recipient sex and age, donor sex, number of CD34+ cells in product and conditioning regimen intensity didn't affect dynamics of immune reconstitution.

Conclusion: Patients undergoing MRD transplantation experience accelerated immune reconstitution, particularly in the first six months post-transplantation.

Keywords: immune reconstitution, allogeneic transplantation, pretransplantation factors

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ZNAČAJ TANDEM TRANSPLANTACIJE MATIČNIH ČELIJA HEMATOPOEZE KOD PACIJENATA SA NOVODIJAGNOSTIKOVANIM MULTIPLIM MIJELOMOM

SIGNIFICANCE OF TANDEM HEMATOPOIETIC STEM CELL TRANSPLANTATION IN PATIENTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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SAŽETAK

Uvod: Autologna transplantacija matičnih ćelija hematopoeze (auto-TMČH) predstavlja standard lečenja pacijenata sa novodijagnostikovanim multiplim mijelomom (NDMM). U cilju optimizacije terapijskog odgovora kod visokorizičnih NDMM primenjuje se tandem auto-TMČH, ali uz veću stopom ranog mortaliteta vezanog za transplantaciju (eng. TRM).

Cilj: Analizirati ukupno preživljavanje (OS), preživljavanje bez progresije (PFS) i stopu posttransplantacionih komplikacija kod pacijenata lečenih jednom (eng. single) i tandem auto-TMČH.

Metode: Retrospektivnom kohortnom studijom obuhvaćeno je 104 pacijenta sa NDMM koji su transplantirani na Klinici za hematologiju UKCS od decembra 2019. do marta 2023.

Rezultati: Medijana starosti u momentu transplantacije je iznosila 54 godine (raspon 30–68). U grupi tandem TMČH 33 od 42 pacijenta su imala R-ISS2 ili R-ISS3. Kod NDMM lečenih tandem vs. single auto-TMČH, OS je bilo 29 meseci (raspon 3–53) vs. 30 meseci (raspon 2–50), $p = 0,058$; PFS u tandem grupi je iznosio 29 meseci (raspon 3–53), a u grupi sa single auto-TMČH 28 meseci (2–50), $p = 0,422$. U tandem grupi bilo je 9 pacijenata koji su nakon auto-TMČH imali progresiju ili relaps bolesti dok je nakon single transplantacije 15 pacijenata imalo progresiju ili relaps, $p = 0,742$. Ukupno je bilo 13 smrtnih ishoda, 9 nakon single auto-TMČH i 4 u grupi tandema, $p = 0,554$. Tri tandem pacijenta su umrli do d+30, $p = 0,063$.

Zaključak: U našoj studiji visokorizični bolesnici sa NDMM lečeni tandem auto TMČH imali su slično OS i PFS uz manju verovatnoću relapsa i veći TRM u odnosu na bolesnike sa koji su lečeni single transplantacijom. To implicira da je tandem auto-TMČH uz nove terapijske modalitete i dalje metoda izbora u lečenju visokorizičnih NDMM.

Ključne reči: multipli mijelom, tandem transplantacija, OS, PFS

ABSTRACT

Introduction: Autologous hematopoietic stem cell transplantation (ASCT) is the standard of care for patients with newly diagnosed multiple myeloma (NDMM). In order to optimize the therapeutic response in high-risk NDMM, tandem-ASCT is applied, but with a higher rate of early mortality related to transplantation (TRM).

Objective: To analyze overall survival (OS), progression-free survival (PFS) and the rate of post-transplantation complications in patients treated with single and tandem-ASCT.

Methods: A retrospective cohort study included 104 patients with NDMM who were transplanted from December 2019 to March 2023.

Results: The median age at the time of transplantation was 54 years (range 30–68). In the tandem group, 33 out of 42 patients had R-ISS2 or R-ISS3. In NDMM tandem vs. single, OS was 29 months (range 3–53) vs. 30 months (range 2–50), $p = 0.058$. PFS in the tandem group was 29 months (range 3–53) vs. single ASCT 28 months (2–50), $p = 0.422$. In the tandem group there were 9 patients who had disease progression or relapse after ASCT, while after single transplantation 16 patients had progression or relapse $p = 0.742$. There was a total of 13 deaths, 9 in the single group and 4 in the tandem group, $p = 0.554$. Three tandem patients died by d+30, $p = 0.063$.

Conclusion: In our study, high-risk patients with NDMM treated with tandem ASCT had similar OS and PFS with a marginally lower probability of relapse and higher TRM compared to patients treated with single transplantation. This implies that tandem ASCT with new therapeutic modalities should remain the standard in the treatment of high-risk NDMM.

Keywords: multiple myeloma, tandem transplantation, OS, PFS

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POREMEĆAJI HEMOSTAZE

HEMOSTASIS AND BLEEDING DISORDERS

HEREDITARY FACTOR XII DEFICIENCY – A CASE REPORT

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SAŽETAK

Uvod: Nedostatak faktora XII (FXII) nasleđuje se autozomno recesivno i retko se sreće u kliničkoj praksi. Najčešće se otkriva slučajno preoperativno tokom rutinskog skrininga kada se nađe produženo aktivirano parcijalno tromboplastinsko vreme (aPTT), a može predstavljati rizik za tromboembolizam kao posledica inaktivacije fibrinolize.

Prikaz slučaja: Prikazujemo slučaj 67-godišnjeg muškarca koji je hospitalizovan radi operativnog lečenja koksartroze i ugradnje endoproteze kuka, kod koga je u testovima hemostaze nađeno veoma produženo aPTT (> 180 s) u dva ponovljena merenja. Operacija je odložena na zahtev ortopeda i tražena je hematološka konsultacija. Pregledom kože nisu utvrđene modrice, petehije i ekhimoze. Ostali fizikalni nalaz bio je uredan. Osim niskog FXII (< 5,9%), ostali faktori i testovi hemostaze bili su u granicama normale. Rotaciona tromboelastografija nije pokazala poremećaj hemostaze. Pre godinu dana bolesnik je hitno operisan zbog perforacije ulkusa i pneumoperitoneuma. Operacija je protekla bez krvarenja i nije zahtevala korekciju faktora koagulacije u perioperativnom periodu. Tom prilikom na kompjuterizovanoj tomografiji abdomena viđena je okluzija leve ilijačne arterije.

Zaključak: Preoperativna priprema pacijenata sa nedostatkom FXII predstavlja izazov. Nasledni poremećaj koagulacije uzrokovan nedostatkom FXII karakteriše in vitro produžena koagulacija krvi bez kliničke tendencije ka krvarenju. Za razliku od nedostataka drugih faktora koagulacije, nedostatak FXII je potpuno asimptomatski i ne uzrokuje prekomerno krvarenje u hiruriji ili kod povreda.

Ključne reči: deficit faktora XII, aktivirano parcijalno tromboplastinsko vreme, krvarenje, tromboza

ABSTRACT

Introduction: Factor XII deficiency (FXII) is inherited in an autosomal recessive manner. It is most often discovered incidentally preoperatively during routine screening when a prolonged activated partial thromboplastin time (aPTT) is found, and may represent a risk for thromboembolism as a consequence of inactivation of fibrinolysis.

Case report: We present the case of a 67-year-old man who was hospitalized for operative treatment of coxarthrosis and implantation of a hip endoprosthesis, in whom hemostasis tests showed a very prolonged aPTT. The operation was postponed at the request of the orthopedist and a hematology consultation was requested. Examination of the skin revealed no bruising, petechiae, or ecchymosis. Systemic examination was normal. Laboratory examination showed an aPTT>180s, which was repeated twice with low FXII < 5.9%. Other factors and the tests of hemostasis were within the normal range. The rotational thromboelastography tests did not show a hemostasis disorder. One year before, the patient was admitted to the clinic and urgent surgery was performed because of ulcer perforation and pneumoperitoneum. The surgery was without bleeding and did not require correction of coagulation factors in the perioperative period. On that occasion, an occlusion of the left iliac artery was seen on the computed tomography of the abdomen.

Conclusion: Hereditary coagulation disorder caused by FXII deficiency is characterized by in vitro delayed blood coagulation without clinical bleeding tendency. Unlike other coagulation factor deficiencies, FXII deficiency is completely asymptomatic and does not cause excessive bleeding in surgery or injuries.

Keywords: factor XII deficiency, activated partial thromboplastin time, bleeding, thrombosis

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UTICAJ TKIVNOG AKTIVATORA PLAZMINOGENA, INHIBITORA AKTIVATORA PLAZMINOGENA-1 I TROMBINOM AKTIVIRANOG FIBRINOLIZNOG INHIBITORA NA RIZIK OD NASTANKA VENSKE TROMBOZE

THE INFLUENCE OF TISSUE PLASMINOGEN ACTIVATOR, PLASMINOGEN ACTIVATOR INHIBITOR-1, AND THROMBIN ACTIVATABLE FIBRINOLYTIC INHIBITOR ON THE RISK OF VENOUS THROMBOSIS

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SAŽETAK

Uvod: Uloga fibrinoliznog mehanizma u riziku za nastanak venske tromboze i dalje je kontroverzna.

Cilj: Cilj rada bio je da se ispita uticaj tkivnog aktivatora plazminogena (t-PA), inhibitora aktivatora plazminogena-1 (PAI-1) i trombinom aktiviranog fibrinoliznog inhibitora (TAFI) na rizik od nastanka prve epizode venske tromboze.

Metode: Istraživanje je obuhvatilo 100 ispitanika sa trombozom dubokih vena i 100 ispitanika bez prethodne istorije venske tromboze. Globalna fibrinolizna aktivnost je procenjena euglobulinskim vremenom lize koaguluma (EVLK). Za određivanje koncentracija t-PA i TAFI korištena je ELISA metoda. Za određivanje koncentracije PAI-1 korišten je metod hromogenog supstrata.

Rezultati: Nije dobijena statistički značajna razlika pri poređenju t-PA i PAI-1 između pacijenata i kontrola. Pacijenti su imali značajno veću koncentraciju TAFI u poređenju sa kontrolama. Analizom relativnog rizika uočeno je trostruko povećanje rizika od venske tromboze povezano sa suprimiranom fibrinoliznom aktivnošću. Osnovni OR bio je 2,70 (95% CI 1,22–5,98) a nakon prilagođavanja za confounding OR je iznosio 3,02 (95% CI 1,26–7,22). Povišene koncentracije TAFI pokazale su uticaj na rizik od nastanka venske tromboze, obizom na osnovni OR od 2,18 (95% CI 1,19–3,99) i prilagođeni OR od 2,25 (95% CI 1,16–4,35), što ukazuje na dvostruko povećanje rizika od nastanka venske tromboze povezano sa povišenom koncentracijom TAFI.

Zaključak: Suprimirana funkcionalnost fibrinoliznog mehanizma trostruko povećava rizik od nastanka tromboze dubokih vena, dok povišen nivo TAFI dvostruko povećava ovaj rizik. Nivo plazminogena, t-PA i PAI-1 nema uticaj na rizik od nastanka venske tromboze.

Ključne reči: fibrinoliza, tromboza dubokih vena, t-PA, PAI-a, TAFI

ABSTRACT

Introduction: The role of the fibrinolytic mechanism in venous thrombosis risk remains controversial.

Objective: To examine the influence of tissue plasminogen activator (t-PA), plasminogen activator inhibitor-1 (PAI-1), and thrombin activatable fibrinolysis inhibitor (TAFI) on the risk of venous thrombosis.

Methods: The research included 100 participants with deep vein thrombosis and 100 participants without venous thrombosis. Global fibrinolytic activity was estimated by euglobulin clot lysis time (ECLT). The ELISA method was used for the determination of t-PA and TAFI concentrations. The chromogenic substrate method was used for the determination of PAI-1 concentrations.

Results: Statistically significant difference was not obtained for t-PA and PAI-1 compared between patients and controls. Patients had significantly higher concentration of TAFI compared to controls. Relative risk analysis showed a three-fold increase in the venous thrombosis risk connected with suppressed fibrinolytic activity. The crude OR was 2.70 (95% CI 1.22–5.98) and adjustments for confounding yielded an OR of 3.02 (95% CI 1.26–7.22). TAFI concentrations showed influence on venous thrombosis risk, as crude OR was 2.18 (95% CI 1.19–3.99) and fully adjusted one stayed in the same range (OR 2.25; 95% CI 1.16–4.35) indicating a two-fold increase in venous thrombotic risk associated with increased TAFI concentrations.

Conclusion: Suppressed functionality of the fibrinolysis mechanism triples the risk of occurrence of deep vein thrombosis while elevated TAFI level doubles the risk of this disease. There is no influence of plasminogen concentrations, t-PA, and PAI-1 levels on venous thrombosis risk.

Keywords: fibrinolysis, deep venous thrombosis, t-PA, PAI-a, TAFI

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NON-FACTOR REPLACEMENT THERAPY: A NEW CHAPTER IN HEMOPHILIA A PROPHYLAXIS

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SAŽETAK

Uvod: Hemofilija A je defICIjencija antihemofilIČnog faktora koja zahteva doživotno lečenje.

Cilj: Analizirali smo efekte profilaktičkog lečenja mimetikom antihemofilIČnog faktora kod deseterice pacijenata sa hemofilijom A.

Metode: Retrospektivna analiza sprovedena je na osnovu podataka o lečenju deset pacijenata muškog pola (četiri dečaka, jednog adolescenta i petorice odraslih) sa teškom hemofilijom A, koji su pre profilaktičkog lečenja emicizumabom profilaktički lečeni koncentratom antihemofilIČnog faktora. Jedan odrasli pacijent razvio je inhibitor tokom profilakse antihemofilIČnim faktorom. Kod četvorice odraslih pacijenata hemofilIčna artropatija razvila se pre početka profilaktičkog lečenja mimetikom antihemofilIČnog faktora. Kod dvojice odraslih pacijenata profilaktičko lečenje emicizumabom sprovodilo se na četiri nedelje, a kod ostalih na dve nedelje. Nakon 14 meseci (u proseku) profilaktičkog lečenja mimetikom antihemofilIČnog faktora analizirali smo broj probojnih krvarenja, godišnju stopu krvarenja, stanje zglobova, neželjene reakcije na emicizumab, kao i stepen zadovoljstva pacijenata lečenjem.

Rezultati: U toku profilakse emicizumabom nije bilo probojnih krvarenja. Nije došlo ni do kliničkog pogoršanja prethodno razvijene hemofilIčne artropatije kod pacijenata sa artropatijom. Vrednost godišnje stope krvarenja bila je jednaka nuli kod svih pacijenata koji su lečeni emicizumabom. Kod naših pacijenata se u toku profilakse emicizumabom nisu javile neželjene reakcije na lek. Svi pacijenti su naveli da su zadovoljniji nesupstitucionim profilaktičkim lečenjem nego supstitucionom profilaksom.

Zaključak: Pružanjem zaštite od probojnih krvarenja i potencijalnim sprečavanjem daljeg oštećenja zahvaćenih zglobova, profilaktičko lečenje emicizumabom omogućava veću aktivnost i povećava kvalitet života lečenih pacijenata.

Ključne reči: hemofilija, antihemofilIČni faktor, emicizumab, inhibitori, profilaksa

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ABSTRACT

Introduction: Hemophilia A is an antihemophilic factor deficiency which requires life-long treatment.

Objective: The purpose of this analysis was to present the effects of prophylactic non-factor replacement therapy in ten patients with hemophilia A.

Methods: This retrospective analysis was conducted on ten male patients (4 children, 1 adolescent, and 5 adults) with severe hemophilia A and a history of antihemophilic factor replacement prophylaxis, prior to the initiation of emicizumab prophylaxis. A single adult patient developed inhibitors during the course of factor replacement prophylaxis. Four adult patients had already developed hemophilic arthropathy before the initiation of non-factor replacement prophylaxis. Two adult patients received emicizumab prophylaxis every four weeks, while others received emicizumab every two weeks. After a 14-month period (average) of non-factor replacement prophylaxis, we analyzed the number of breakthrough bleeding episodes, annualized bleeding rate, involvement of target joints, adverse drug reactions, and interviewed the patients regarding their satisfaction with the non-factor replacement treatment.

Results: None of the patients on emicizumab prophylaxis experienced breakthrough bleeding or clinical worsening of the affected target joints during the period of emicizumab prophylaxis. Annualized bleeding rate was zero in all patients on emicizumab prophylaxis. No adverse drug reactions occurred in our patients during emicizumab prophylaxis. All patients reported greater treatment satisfaction compared to the replacement prophylaxis.

Conclusion: By providing safety from bleeding events and potentially the stability of the affected joints, emicizumab prophylaxis enables greater activity and increases the quality of life of treated patients.

Keywords: hemophilia, antihemophilic factor, emicizumab, inhibitors, prophylaxis

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DIFFERENCES IN FIBRINOLYTIC PROFILE BETWEEN PATIENTS WITH DIFFERENT LOCALIZATIONS AND TYPES OF VENOUS THROMBOSIS

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SAŽETAK

Uvod: Uloga fibrinolize u venskoj trombozi (VT) još uvek nije razjašnjena.

Cilj: Cilj studije je ispitivanje razlika u globalnoj funkcionalnosti fibrinoliznog mehanizma i njegovim pojedinačnim komponentama između pacijenata sa različitim tipovima i lokalizacijama venskih tromboza i zdravih osoba.

Metode: Uzorak je obuhvatio 100 pacijenata sa dijagnozom VT i 100 zdravih kontrola. Pacijenti su grupisani u odnosu na tip venske tromboze (spontana ili provocirana) i u odnosu na lokalizaciju (distalna, proksimalna i atipična). Euglobulinsko vreme lize koaguluma (EVLK) korišteno je za procenu globalne fibrinolizne funkcionalnosti, a određivane su i koncentracije plazminogena, tkivnog aktivatora plazminogena (t-PA), trombinom aktiviranog fibrinoliznog inhibitora (TAFI) i inhibitora aktivatora plazminogena-1 (PAI-1).

Rezultati: Pacijenti sa izolovanom distalnom i provociranom VT imaju značajno duže EVLK u poređenju sa kontrolama ($218,32 \pm 41,12$ min vs. $185,62 \pm 42,30$ min, $p = 0,001$ i $208,18 \pm 48,53$ min vs. $185,62 \pm 42,30$ min, $p = 0,018$). Pacijenti sa provociranom VT imaju više nivoe plazminogena ($127,14 \pm 27,73\%$ vs. $117,09 \pm 24,49\%$, $p = 0,044$) i t-PA ($20,02 \pm 11,07$ ng/ml vs. $16,78 \pm 8,08$ ng/ml, $p = 0,042$) u poređenju sa kontrolama. TAFI je značajno viši kod provociranih ($19,93 \pm 3,97$ ng/ml vs. $17,13 \pm 4,25$ ng/ml, $p = 0,000$), spontanih ($19,53 \pm 5,97$ ng/ml vs. $17,13 \pm 4,25$ ng/ml, $p = 0,023$), izolovanih distalnih ($20,72 \pm 4,96$ ng/ml vs. $17,13 \pm 4,25$ ng/ml, $p = 0,001$) i proksimalnih ($19,37 \pm 5,33$ ng/ml vs. $17,13 \pm 4,25$ ng/ml, $p = 0,013$) VT, u poređenju sa kontrolama.

Zaključak: Postoje značajne razlike u fibrinoliznom mehanizmu između bolesnika sa različitim tipovima i lokalizacijama venskih tromboza u poređenju sa zdravim osobama.

Ključne reči: fibrinoliza, plasminogen, tromboza, trombinom aktivirani fibrinolizni inhibitor

ABSTRACT

Introduction: The role of the fibrinolytic mechanism in venous thrombosis (VT) remains incompletely understood.

Objective: This study aimed to investigate the functionality of the fibrinolytic system and its components in patients with various types and locations of VT compared to a healthy control group.

Methods: The case group comprised 100 patients with VT and 100 healthy controls. Patients were categorized based on VT type (spontaneous vs. provoked) and location (distal, proximal, and atypical). Euglobulin clot lysis time (ECLT) assessed global fibrinolytic functionality, while specific components measured included plasminogen, tissue plasminogen activator (t-PA), thrombin-activatable fibrinolysis inhibitor (TAFI), and plasminogen activator inhibitor-1 (PAI-1).

Results: Patients with isolated distal VT and provoked VT showed significantly prolonged ECLT compared to controls (218.32 ± 41.12 min vs. 185.62 ± 42.30 min, $p = 0.001$; 208.18 ± 48.53 min vs. 185.62 ± 42.30 min, $p = 0.018$, respectively). Provoked VT patients had higher plasminogen ($127.14 \pm 27.73\%$ vs. $117.09 \pm 24.49\%$, $p = 0.044$) and t-PA levels (20.02 ± 11.07 ng/ml vs. 16.78 ± 8.08 ng/ml, $p = 0.042$) compared to controls. TAFI levels were significantly elevated in provoked VT (19.93 ± 3.97 ng/ml vs. 17.13 ± 4.25 ng/ml, $p = 0.000$) and spontaneous VT (19.53 ± 5.97 ng/ml vs. 17.13 ± 4.25 ng/ml, $p = 0.023$), as well as in isolated distal (20.72 ± 4.96 ng/ml vs. 17.13 ± 4.25 ng/ml, $p = 0.001$) and proximal (19.37 ± 5.33 ng/ml vs. 17.13 ± 4.25 ng/ml, $p = 0.013$) VT, compared to controls.

Conclusion: Significant variations exist in the fibrinolytic mechanism across different types and locations of venous thrombosis compared to healthy individuals.

Keywords: fibrinolysis, plasminogen, thrombosis, thrombin-activatable fibrinolysis inhibitor

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ŽIVOTNO UGROŽAVAJUĆE GASTROINTESTINALNO KRVARENJE KOD PACIJENTKINJE SA VON WILLEBRAND-OVOM BOLESTI – PRIKAZ SLUČAJA

LIFE-THREATENING GASTROINTESTINAL BLEEDING IN PATIENT WITH VON WILLEBRAND DISEASE – A CASE REPORT

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SAŽETAK

Uvod: Bolesnici oboleli od tipa 2 i 3 von Willebrand-ove bolesti (vWb) imaju povećan rizik od gastrointestinalnog (GIT) krvarenja, a istraživanja pokazuju da je najčešći razlog pojava angiodisplazija GIT-a. Profilaktička primena faktora se nije pokazala jednako uspešnom u prevenciji sluzničnog krvarenja, poput onog iz GIT, kao u prevenciji zglobnih krvarenja.

Prikaz slučaja: Bolesnici starosti 65 godina dijagnoza ulceroznog kolitisa postavljena je 2011. godine. Zbog imunorefraktnosti i kortikozavisnog oblika bolesti u aprilu 2017. godine započeta je biološka terapija. Od 2019. je na terapiji vedolizumabom i u remisiji. vWb tip 3 je dokazana tokom bolničkog lečenja zbog recidiva GIT krvarenja 2019. godine. Od novembra iste godine profilaktički prima FVIII sa povišenim koncentracijama vWF u dozi od 2000 i.j. tri puta nedeljno. U maju 2023. godine je hospitalizovana zbog hematohezeje i melene, sa razvojem hemoragijskog šoka (FVIII 30,1%, vWf act < 4%, vWf Ag 22,5%, Hgb 67 g/L). Ordinirani su preparati FVIII sa povišenim koncentracijama vWF u dozi od 50 i.j./kg/12h u trajanju od 14 dana. Ezofagogastroduodenoskopijom je viđen plići ulkus promera 7mm u antrumu želuca, te su plasirane četiri hemoklipse, na šta dolazi do prestanka krvarenja i stabilizacije opšteg stanja. CT angiografijom nije utvrđeno ishodište krvarenja koje bi koreliralo sa ovakvom kliničkom slikom.

Zaključak: Recidivi životno ugrožavajućeg krvarenja se mogu javiti i pored profilaktičke primene preparata vWF. Neophodan je multidisciplinarni pristup u pružanju optimalnog tretmana ovim bolesnicima.

Ključne reči: Von Willebrand faktor, profilaksa, gastrointestinalno krvarenje

ABSTRACT

Introduction: Patients with type 2 and 3 von Willebrand disease (vWD) have a higher risk of gastrointestinal (GIT) bleeding, supposedly due to GIT angiodysplasia. According to published data prophylaxis with vWF concentrate for mucosal bleeding, such as GI bleeding, was not found to be as effective as for joint bleeding.

Case report: A 65-year-old female patient was diagnosed with ulcerous colitis in 2011. Due to an immune-refractory and corticosteroid-dependent form of disease in 2017, the patient was treated with biological therapy. In 2019 vedolizumab treatment was started and remission was achieved. vWD type 3 was proven during hospitalization for GIT hemorrhage recurrence in 2019. Prophylaxis with vWF concentrates was started (2000 IU three times a week) in November 2019. In May 2023, the patient was admitted to the hospital due to hematochezia and melena, with the development of hemorrhagic shock (FVIII 30.1%, vWf act < 4%, vWf Ag 22.5%, Hgb 67 g/L). Replacement therapy with FVIII/vWf concentrates (50 IU/kg/12 h) was administered over 14 days. Esophagogastroduodenoscopy revealed a shallow ulcer of 7 mm in radius, and four hemoclipses were administered, stopping the bleeding. CT angiography was performed without a clear origin of bleeding, that would correlate with the clinical presentation.

Conclusion: Life threatening mucosal bleeding can happen despite prophylaxis with vWF. The importance of multidisciplinary approach in providing optimal treatment to these patients is essential.

Keywords: Von Willebrand Factor, prophylaxis, gastrointestinal hemorrhage

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KLINIČKE I DEMOGRAFSKE KARAKTERISTIKE BOLESNIKA SA STEČENOM HEMOFILIJOM A LEČENIH U KLINICI ZA HEMATOLOGIJU UNIVERZITetskOG KLINIČKOG CENTRA SRBIJE U PERIODU OD 2009. DO 2024. GODINE

CLINICAL AND DEMOGRAPHIC CHARACTERISTICS OF PATIENTS WITH ACQUIRED HEMOPHILIA A TREATED AT THE HEMATOLOGY CLINIC OF THE UNIVERSITY CLINICAL CENTER OF SERBIA IN THE PERIOD FROM 2009 TO 2024

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SAŽETAK

Uvod: Stečena hemofilija A (SHA) je bolest sa izrazitom sklonošću krvarenju usled prisustva autoantitela usmerenih na FVIII. Od presudnog značaja za ishod lečenja SHA je rano prepoznavanje, zbog čega su podaci o načinu prezentacije i kliničkim karakteristikama ovih bolesnika od velike važnosti.

Cilj: Analizirati kliničke i demografske karakteristike bolesnika sa SHA koji su lečeni u Klinici za hematologiju u periodu 1.7.2009. godine do 1.7.2024. godine.

Metode: Retrospektivna analiza podataka dostupnih iz medicinskih istorija bolesnika sa SHA koji su dijagnostikovani i lečeni u Klinici za hematologiju Univerzitetskog kliničkog centra Srbije u periodu od 1.7.2009. do 1.7.2024. godine. Prikupljeni podaci su prikazani merama deskriptivne statistike.

Rezultati: U periodu od 15 godina, dijagnoza SHA je postavljena kod 24 bolesnika. Medijana starosti na prezentaciji je bila 70,5 godina (opseg 20,87). Od ukupnog broja obolelih 54% (13 bolesnika) su bile žene. Kod dve bolesnice (8%) dijagnoza SHA je postavljena u postpartalnom periodu. U našoj grupi bolesnika najčešći način prezentacije je bilo krvarenje u kožu i sluzokože (65%). Veliko krvarenje po ISTH kriterijumima je pri dijagnozi imalo 13 bolesnika (54%). Medijana od pojave prvih simptoma do postavljanja dijagnoze je iznosila 14 dana (opseg 1,87) s tim da kod jednog bolesnika iz medicinske dokumentacije nije bilo moguće ustanoviti kada su tačno prvi simptomi počeli.

Zaključak: U našoj grupi bolesnika SHA je bolest starijeg životnog doba, koja se javlja kod oba pola sa podjednakom učestalošću. Iako se kod čak polovine bolesnika SHA prezentovala velikim krvarenjem medijana do postavljanja dijagnoze je iznosila 14 dana.

Ključne reči: stečena hemofilija A, kliničke karakteristike, demografski podaci

ABSTRACT

Introduction: Acquired hemophilia A (AHA) is a disease with a marked bleeding tendency due to FVIII autoantibodies. Early recognition is crucial for the AHA outcome. Therefore, data on these patients' presentation and clinical characteristics are essential.

Objective: To analyze the clinical and demographic characteristics of AHA patients treated at the Hematology Clinic from July 1, 2009 to July 1, 2024.

Methods: Retrospective analysis of data available from the medical histories of AHA patients who were diagnosed and treated at the Hematology Clinic of the University Clinical Center of Serbia from July 1, 2009, to July 1, 2024. The collected data are presented using descriptive statistics.

Results: In 15 years, 24 patients with AHA were diagnosed. Median age at presentation was 70.5 years (range 20.87). Of the total number of patients, 54% (13 patients) were women. In two patients (8%), AHA was established postpartum. In our patients, the most common presentation was bleeding into the skin and mucous membranes (65%). At the diagnosis, 13 patients (54%) had "major" bleeding according to ISTH criteria. The median time from the first symptoms to the diagnosis was 14 days (range 1.87). In one patient, it was impossible to determine when exactly the first symptoms began from the medical records.

Conclusion: In our group of patients, AHA is a disease of older age, which occurs in both sexes with equal frequency. Although in as many as half of the patients, AHA presented with "major" bleeding, the median time until diagnosis was 14 days.

Keywords: acquired hemophilia A, clinical characteristics, demographic data

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ACQUIRED VON WILLEBRAND SYNDROME IN PATIENT WITH CHRONIC LYMPHOCYTIC LEUKEMIA – CLINICAL CASE

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SAŽETAK

Uvod: Stečeni von Willebrandov sindrom (vWS) predstavlja redak poremećaj hemostaze često povezan sa limfoproliferativnim, mijeloproliferativnim i kardiovaskularnim bolestima.

Prikaz slučaja: U junu 2021. kod pacijenta starog 68 godina dijagnostikovala se je hronična limfocitna leukemija (HLL). Na prezentaciji: Le 44x10⁹/L, Hb 104 g/L, Tr 146x10⁹/L; limfadenopatija do 3 cm; palpabilna splenomegalija 3cm. Zbog produženog aPTT, dodatnom dijagnostikom detektovan je težak deficit von Willebrandovog faktora (vWF) – vWF Ac 6%. Krvarenje (melena) se prvi put javilo u septembru 2021. U laboratorijskim analizama: Le 138x10⁹/L, Hb 45 g/L, Tr 159x10⁹/L, vWF Ac 6%. Po stabilizaciji krvarenja primenom humanog vWF, lečen primenom obinutuzumab-hlorambucil protokola. Zbog ponavljanih gastrointestinalnih krvarenja učinjena endoskopska ispitivanja i CT angiografija, bez utvrđivanja lokalizacija krvarenja. Primena hemioterapije obustavljena je zbog rektoragije. Video kapsulom je detektovano krvarenje u distalnoj trećini ileuma. Dalje lečenje nastavljeno je primenom imunohemioterapije u februaru 2022., komplikovano hematurijom i infekcijom *C. difficile* praćene rektoragijom. Zbog otoka desne noge na mestu plasiranog centralnog venskog katetera urađen je kolor dopler krvnih sudova kojim je potvrđena tromboza ilijačne, femoralne, poplitealne i kruralne vene. Po izostanku hemoragijskog sindroma, primenjen je drugi ciklus imunohemioterapije, uz primenu niskomolekularnog heparina, a humani vWF primenjivan samo u slučaju krvarenja. Primena trećeg ciklusa hemioterapije komplikovala se ponovnom klostrijalnom infekcijom, rektoragijom i pancitopenijom, nakon čega je u julu 2022. nastupio smrtni ishod.

Zaključak: Lečenje stečenog vWS podrazumeva lečenje oboljenja koje ga uzrokuje. Istovremena pojava tromboze i stečenog vWS predstavlja poseban izazov.

Ključne reči: vWS, HLL, tromboza, krvarenje

ABSTRACT

Introduction: Acquired von Willebrand syndrome (vWS) is a rare bleeding disorder often linked to lymphoproliferative, myeloproliferative, and cardiovascular disorders.

Case report: In June 2021, chronic lymphocytic leukemia (CLL) was diagnosed in a 68-year-old male. At presentation: WBC 44x10⁹/L, Hb 104 g/L, Plt 146x10⁹/L; lymphadenopathy up to 3 cm; palpable splenomegaly 3cm. Due to prolonged aPTT, further diagnostics revealed severe von Willebrand factor (vWF) deficiency – vWF Ac 6%. Bleeding (melena) first occurred in September 2021 (WBC 138x10⁹/L, Hb 45 g/L, Plt 159x10⁹/L, vWF Ac 6%). After stabilizing the bleeding with human vWF treatment, obinutuzumab and chlorambucil protocol was administered. Recurrent gastrointestinal bleeding prompted endoscopic investigations and CT angiography, without identification of the bleeding source, leading to chemotherapy cessation due to rectal bleeding. Capsule endoscopy detected bleeding in the distal third of the ileum. Further treatment with immunotherapy in February 2022 was complicated by hematuria, *C. difficile* infection and rectal bleeding. Swelling of the right leg at the central venous catheter site led to a color Doppler ultrasound confirming thrombosis in the iliac, femoral, popliteal, and crural veins. After the resolution of hemorrhagic syndrome, second cycle of immunotherapy along with low molecular weight heparin were administered, with use of human vWF only in case of bleeding. Further chemotherapy complicated with recurrent Clostridium infection, rectal bleeding and pancytopenia, culminating in a fatal outcome in July 2022.

Conclusion: Managing acquired vWS requires treating the underlying disorder while concurrent thrombosis presents a unique challenge in clinical management.

Keywords: vWS, CLL, thrombosis, bleeding

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HEPCIDIN IS A BETTER MARKER OF THE TYPE OF ANEMIA IN ANTIPHOSPHOLIPID SYNDROME RELATIVE TO FERRITIN LEVEL

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SAŽETAK

Uvod: Etiologija anemije u antifosfolipidnom sindromu je raznolika i teško je utvrditi.

Cilj: Poređena je korist markera metabolizma gvožđa u kontekstu inflamatornih markera kao što su IL6 i hsCRP u utvrđivanju vrste anemije između pacijenata sa primarnim AFS (PAFS) i onih sa AFS udruženim sa SLE (SAFS).

Metode: U studiji je učestvovalo 122 AFS pacijenta (79 AFS i 47 SAFS). Merena je koncentracija markera metabolizma gvožđa (Hgb, er, MCV, Fe, TIBC, feritin, hepcidin) i korelirana sa vrednostima inflamatornih markera.

Rezultati: Nije bilo statistički značajne razlike u vrednostima hemoglobina ($p = 0,202$), er ($p = 0,332$), MCV ($p = 0,860$), Fe ($p = 0,744$), Fe/TIBC ($p = 0,861$), feritina ($p = 0,749$) i hsCRP ($p = 0,449$) između PAFS i SAFS pacijenata. Postojala je statistički značajna razlika u nivou hepcidina ($17,13 \pm 4,57$ vs. $16,21 \pm 5,46$, $p = 0,02$) i IL6 (med 1,31 vs. med 2,02, $p = 0,001$) između ovih grupa. Nivo feritina je korelirao sa IL6 i hsCRP ($p = 0,029$ i $0,015$) nasuprot nivou hepcidina ($p > 0,05$). Ako se koristi granica feritina višeg od 15 za anemiju hronične bolesti, bilo je 81,9% ovih vrednosti bez razlike u PAFS i SAFS grupi. Ova granična vrednost je pozitivno korelirala sa IL6 ($p = 0,016$) kao sa vrednosti hepcidina ($p = 0,045$).

Zaključak: Feritin je dobar pokazatelj vrste anemije u AFS, ali je u tesnoj korelaciji sa inflamatornim markerima, pa je kao reaktant akutne faze manje pouzdan u utvrđivanju vrste anemije. Hepcidin je bolji inikator vrste anemije pošto inflamatorni markeri imaju manji uticaj na njega.

Ključne reči: feritin, hepcidin, anemija, antifosfolipidni sindrom

ABSTRACT

Introduction: The assessment of anemia etiology in patients with APS can be challenging.

Objective: We compared utility of iron metabolism markers in the context of inflammatory markers as hsCRP and IL6 between primary APS and APS associated to SLE (SAPS).

Methods: The study involved 122 APS patients [79 PAPS and 47 SAPS patients]. Iron metabolism markers such as hgb, er, MCV, Fe, TIBC, ferritin, hepcidin were measured and correlated to inflammatory markers.

Results: There were not statistically significant differences considering levels of hemoglobin ($p = 0,202$), er ($p = 0,332$), MCV ($p = 0,860$), Fe ($p = 0,744$), Fe/TIBC ($p = 0,861$), ferritin ($p = 0,749$) and hsCRP ($p = 0,449$) between PAPS and SAPS groups. There were statistically significant differences considering hepcidin level ($17,13 \pm 4,57$ vs. $16,21 \pm 5,46$, $p = 0,02$) and IL6 level (med 1,31 vs. med 2,02, $p = 0,001$) between these two groups. Level of ferritin correlated to IL6 and hsCRP ($p = 0,029$ and $0,015$) as opposed to level of hepcidin ($p > 0,05$). If using a ferritin cutoff of greater than 15 for anemia of chronic disease, there were 81,9% of these values without difference between PAPS and SAPS groups. This cut off positively correlated to IL6 ($p = 0,016$) as to hepcidin level ($p = 0,045$).

Conclusion: Ferritin is a good indicator of the type of anemia in APS, but it tightly correlates to inflammatory markers as a reactant of the acute phase and in that sense, it is less reliable. Hepcidin is a better indicator of the type of anemia with less influence of inflammation on its value.

Keywords: ferritin, hepcidin, anemia, antiphospholipid syndrome

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RESULTS OF EMICIZUMAB ADMINISTRATION FOR PREVENTION OF BLEEDING IN ADULT PATIENTS WITH HEMOPHILIA A IN THE REPUBLIC OF SERBIA

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SAŽETAK

Uvod: Emicizumab je humanizovano bispecifično antitelo IgG4 klase koje obavlja funkciju aktiviranog FVIII. Lek se koristi za redovnu prevenciju krvarenja kod bolesnika sa teškom formom hemofilije A sa ili bez inhibitora. Iako su kliničke studije pokazale visoku efikasnost i bezbednost primene emicizumaba, malo je podataka o efektima primene ovog leka u realnoj kliničkoj praksi.

Cilj: Analiza podataka o karakteristikama odraslih bolesnika koji koriste emicizumab u R. Srbiji, o njegovoj efikasnosti i bezbednosti u realnoj kliničkoj praksi.

Metode: Retrospektivno su ispitivane karakteristike odraslih bolesnika koji su lečeni emicizumabom u 4 tercijarna centra u R. Srbiji. Analizirana je učestalost krvarenja pre i nakon uvođenja emicizumaba za bolesnike koji su dobijali ovaj lek u trajanju od najmanje 24 nedelje.

Rezultati: Zaključno sa 01.06.2024. godine, primenom emicizumaba lečeno je 36 bolesnika sa teškom formom hemofilije A (27 bez inhibitora i 9 sa inhibitorima). Medi-jana trajanje terapije kod bolesnika sa inhibitorima bila je 46 (44–48), a kod bolesnika bez inhibitora 10 (1–24) meseci. U toku 12 meseci pre uvođenja emicizumaba u terapiju, bez krvarenja u zglobove bilo je 28% bolesnika bez inhibitora i 22% bolesnika sa inhibitorom, a u toku primene ovog leka zglobna krvarenja nisu registrovana kod 93% bolesnika bez inhibitora i 77% bolesnika sa inhibitorom. Ozbiljni neželjeni događaji u toku primene emicizumaba zabeleženi su kod 3 bolesnika, ali nije potvrđena sigurna veza između primene leka i neželjenog događaja.

Zaključak: Naši rezultati ukazuju na visoku efikasnost emicizumaba u svakodnevnoj kliničkoj praksi koja je uporediva sa rezultatima iz registracionih kliničkih studija.

Ključne reči: hemofilija, emicizumab, profilaksa, krvarenje

ABSTRACT

Introduction: Emicizumab is a humanized bispecific antibody of the IgG4 class that mimics activity of FVIIIa. It is used for regular prevention of bleeding in patients with a severe form of hemophilia A with or without inhibitors. Although clinical studies have shown the high efficiency and safety of emicizumab, real-world data are scarce.

Objective: Analysis of data on the number of adult patients using emicizumab in the Republic of Serbia, and its effectiveness and safety in real clinical practice.

Methods: The characteristics of adult patients treated with emicizumab in 4 tertiary centers in the Republic of Serbia were retrospectively investigated. For patients receiving this drug for at least 24 weeks, the frequency of bleeding before and after the introduction of emicizumab was analyzed.

Results: In total, 36 patients with a severe form of hemophilia A were treated with emicizumab (27 without and 9 with inhibitors) until June 01, 2024. The median duration of therapy in inhibitor patients was 46 (44–48), and in non-inhibitor patients 10 (1–24) months. During the 12 months before the start of emicizumab administration, zero joint bleeds were experienced in 28% of non-inhibitor patients and 22% of inhibitor patients, compared to 93% of non-inhibitor and 77% of inhibitor patients in the period after the start of emicizumab treatment. Serious adverse events were recorded in 3 patients, but a firm relation between emicizumab and the adverse event was not confirmed.

Conclusion: Our data indicate a high efficiency of emicizumab in daily clinical practice, which is comparable to the results from registration clinical studies.

Keywords: haemophilia, emicizumab, prophylaxis, bleeding

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ENDOTHELIAL DYSFUNCTION CORRELATES TO CONCENTRATION OF ASYMETRIC DIMETHYLARGININE AND CRP IN ANTIPHOSPHOLIPID SYNDROME PATIENTS

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SAŽETAK

Uvod: U antifosfolipidnom sindromu (AFS) je dokazano postojanje endotelne disfunkcije i to kako u primarnom tako i u sekundarnom (PAFS/SAFS).

Cilj: Utvrditi korelaciju koncentracije asimetričnog dimetilarginina (ADMA) i C reaktivnog proteina (hsCRP) endotelnoj difunkciji u AFS što nije u potpunosti do sada ispitano.

Metode: U studiji je učestvovalo 145 AFS (59 PAFS i 46 SAFS) pacijenata i upoređivani sa kontrolnom grupom od 40 zdravih. Prisustvo endotelne disfunkcije je procenjeno merenjem protoka brahijalna arterije (FMD, flow mediated dependent dilatation). ADMA (micromol/L) i hsCRP (mg/L) su određivani kod svih učesnika u studiji.

Rezultati: Pokazano je da je FMD kod pacijenata sa AFS značajno snižena u odnosu na kontrolnu grupu ($p < 0,001$), bez značajne razlike između PAFS i SAFS grupe. ADMA i hsCRP su značajno više kod AFS pacijenata u odnosu na kontrolnu grupu ($p < 0,001/p = 0,006$), kao i kod SAFS u odnosu na PAFS grupu ($p < 0,001/p = 0,022$). FMD je u korelaciji sa ADMA ($p = 0,472, p < 0,001$) i sa hsCRP ($p = 0,181, p = 0,033$). Koncentracije hsCRP i ADMA pokazuju pozitivnu korelaciju ($p = 0,190, p = 0,025$). Od svih antifosfolipidnih antitela, titar $\beta 2$ GPI je pokazao statistički značajnu korelaciju sa oba: ADMA ($p = 0,193, p = 0,049$) i hsCRP ($p = 0,225, p = 0,024$). U regresionom modelu, ADMA je potvrdila svoj uticaj na FMD (B 0,518, SE 0,183, Wald 8,041, $p = 0,005$, Exp(B) 1,679, 95% CI 1,174–2,402).

Zaključak: ADMA i hsCRP bi mogli da se koriste kao jednostavni i jeftini pokazatelji prisustva endotelne disfunkcije kod pacijenata sa AFS.

Ključne reči: endotelna disfunkcija, antifosfolipidni sindrom, asimetrični dimetilarginin, C reaktivni protein

ABSTRACT

Introduction: It has been demonstrated that endothelial dysfunction is impaired in both, primary and secondary antiphospholipid syndrome (PAPS/SAPS).

Objective: The potential contribution of asymmetric dimethylarginine (ADMA) and high-sensitivity C reactive protein (hsCRP) to endothelial dysfunction (ED) in APS patients has not been studied in detailed so far.

Methods: The study involved 145 APS patients (59 PAPS and 46 SAPS patients) compared to 40 age and sex matched controls. Endothelial dysfunction was assessed by measurement of flow mediated dilatation (FMD, endothelium-dependent function) of the brachial artery. ADMA (micromol/L) and hsCRP (mg/L) were measured in all patients.

Results: It was found that FMD in patients with APS was significantly lower than those of the controls ($p < 0.001$), without difference between PAPS and SAPS group. ADMA and hsCRP concentrations were significantly higher in the patient cohort than in the control group ($p < 0.001, p = 0.006$ respectively), as in the SAPS comparing to PAPS group ($p < 0.001, p = 0.022$ respectively). FMD impairment correlated to ADMA ($p = 0.472, p < 0.001$) and to hsCRP ($p = 0.181, p = 0.033$). Levels of hsCRP and ADMA showed positive correlation ($p = 0.190, p = 0.025$). Among all antiphospholipid antibodies (aPL) types and titer, only $\beta 2$ GPI showed correlation to both: ADMA ($p = 0.193, p = 0.049$) and hsCRP ($p = 0.225, p = 0.024$). In regression model, ADMA concentration confirmed the strength of its association (B 0.518, SE 0.183, Wald 8.041, $p = 0.005$, Exp(B) 1.679, 95% CI 1.174–2.402).

Conclusion: ADMA and hsCRP may be used as a simple and low-cost tools for the presence of endothelial dysfunction in APS patients.

Keywords: endothelial dysfunction, antiphospholipid syndrome, asymmetric dimethylarginine, C reactive protein

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THE ASSOCIATION BETWEEN THROMBOCYTOPENIA AND THYROTOXICOSIS

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SAŽETAK

Uvod: U medicinskoj literaturi opisana je povezanost tireotoksikoze i trombocitopenije, iako smjernice ne preporučuju skrining na bolesti štitaste žlijezde kod pacijenta sa trombocitopenijom. Poznato je da hipertireoza dovodi do trombocitopenije povećanjem retikuloendotelijalne aktivnosti i te trombocitopenije budu uglavnom blage do umjerene.

Prikaz slučaja: Prikazaćemo pacijentkinju starosti 66 godina koja je liječena u Centru za kardiohirurgiju zbog rekonstrukcije mitralne i trikuspidalne valvule, a od ranije liječi atrijalnu fibrilaciju. Tokom navedene hospitalizacije verifikovana tireotoksikoza, uz negativna TRAb antitijela. Ultrazvučnim pregledom štitaste žlijezde verifikovana polinodозна struma sa heteroehogenim nodusom u lijevoj reznju dimenzija 37x25x29 mm koji zahtijeva operativno liječenje. Pacijentkinja se od ranije liječi od strane hematologa zbog trombocitopenije, bez manifestacija hemoragijskog sindroma. U razmazu periferne krvi viđena anizopoikilocitoza eritrocita, 45% segmentnih neutrofila, 1% eozinofila, 48% limfocita, 6% monocita, uz rijetke, gigantske trombocite, bez prisustva blasta. Serološke analize na bakterije i viruse pristigle su negativne, kao i imunoserologija na antifosfolipidni sindrom uz ANA nukleolarni tip 1+. Pacijentkinja inicijalno tretirana kortikosteroidima uz postizanje remisije, ali u daljem toku dolazi do relapsa bolesti, uz parcijalni odgovor na primjenu kortikosteroida. S obzirom na to da se radi o pacijentkinji koja je kardiološki bolesnik, kao i da je zbog neophodnosti primjene oralne antikoagulantne terapije i pripreme za operativno liječenje nodusa štitaste žlijezde potrebno da broj trombocita bude iznad 30, odlučeno je da se u terapiju uvede Rituximab u nedeljnim ciklusima.

Zaključak: Prema svemu navedenom zaključujemo da se kod pacijentkinje radi o tireotoksikozi na terenu toksičnog nodusa, uz imunološke trombocitopeniju čije je liječenje kompleksno, a naročito kod kardioloških pacijenata.

Ključne reči: tireotoksikoza, toksični nodus, trombocitopenija, atrijalna fibrilacija

ABSTRACT

Introduction: In medical literature, a connection between thyrotoxicosis and thrombocytopenia has been described, although guidelines do not recommend screening for thyroid diseases in patients with thrombocytopenia. Hyperthyroidism can lead to thrombocytopenia by increasing reticuloendothelial activity, usually resulting in mild to moderate thrombocytopenia.

Case report: We present a 66-year-old female patient treated at the Cardiac Surgery Center for mitral and tricuspid valve reconstruction, with a history of atrial fibrillation. During hospitalization, thyrotoxicosis was confirmed, with negative TRAb antibodies. Ultrasound examination revealed multinodular goiter with a hypoechoic nodule in the left lobe measuring 37x25x29 mm, requiring surgery. The patient was also treated by a hematologist for thrombocytopenia without hemorrhagic syndrome. A peripheral blood smear showed anisopoikilocytosis of erythrocytes, 45% segmented neutrophils, 1% eosinophils, 48% lymphocytes, 6% monocytes, with rare giant platelets, and no blasts. Serological tests for bacteria, viruses, and immunoserology for antiphospholipid syndrome were negative, except for ANA nucleolar type 1+. The patient was initially treated with corticosteroids, achieving remission, but later relapsed, showing a partial response to corticosteroids. Due to the patient's cardiac condition and the need for oral anticoagulant therapy and preparation for thyroid nodule surgery, it was essential to maintain a platelet count above 30. Therefore, Rituximab was introduced in weekly cycles.

Conclusion: In conclusion, this patient has thyrotoxicosis due to a toxic nodule and immunological thrombocytopenia, which is very challenging to manage, especially in patients with heart disease.

Keywords: thyrotoxicosis, toxic nodule, thrombocytopenia, atrial fibrillation

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LEČENJE IDIOPATSKE TROMBOCITOPENIJE PRIMENOM TPO AGONISTA I FARMAKOEKONOMSKI ASPEKT – ISKUSTVO NAŠEG CENTRA

TREATMENT OF IDIOPATHIC THROMBOCYTOPENIA USING TPO AGONISTS AND PHARMACOECONOMIC ASPECT – EXPERIENCE OF OUR CENTER

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SAŽETAK

Uvod: Primena trombopoetinskih agonista (TPO) u lečenju idiopatske trombocitopenije (ITP) omogućava izbegavanje primene imunosupresivne terapije.

Cilj: Analiza upotrebe TPO agonista na Klinici za hematologiju, Univerzitetskog kliničkog centra Vojvodine i osvrtnje na farmakoekonomski aspekt primene ovih lekova.

Metode: Retrospektivnom opservacionom studijom je obuhvaćeno 25 bolesnika obolelih od hronične ITP, a lečenih primenom TPO agonista u periodu 2018–2024. godine. Podaci o cenama TPO agonista dobijeni su iz Registra prometa i potrošnje lekova ALIMIS.

Rezultati: U navedenom periodu je TPO agonistima lečeno ukupno 25 bolesnika obolelih od hronične ITP. Od ukupnog broja 84% je inicijalno lečeno primenom eltrombopaga, a 16% primenom romiplostima. Kod 6 bolesnika eltrombopag je zamenjen romiplostimom (kod tri zbog izostanka odgovora, a kod tri zbog nuspojave leka). Nakon 12 nedelja odgovor je postiglo 72% bolesnika, od kojih je 72% imalo $\geq 100 \times 10^9/L$, 22% ≥ 50 a $< 100 \times 10^9/L$ i 6% ≥ 30 a $< 50 \times 10^9/L$ trombocita. Prosečna dužina lečenja TPO agonistima iznosi 9, a dužina trajanja terapijskog odgovora nakon njihovog isključenja iznosi 8 meseci. Dva bolesnika imala su neželjenu reakciju u vidu hepatotoksičnosti, a dva izražene bolove u kostima i mišićima što je bio razlog njihovog odustajanja od terapije. Prosečni troškovi primene TPO agonista po jednom lečenom pacijentu za jun 2024. godine iznose 1299,2 € za eltrombopag, odnosno 1560 € za romiplostim.

Zaključak: Ovi lekovi pored svoje terapijske efikasnosti, predstavljaju značajno finansijsko opterećenje, zbog čega je neophodno načiniti individualizaciju procene dužine trajanja lečenja i momenta obustavljanje terapije TPO agonistima.

Ključne reči: eltrombopag, romiplostim, TPO agonisti

ABSTRACT

Introduction: The use of thrombopoietin agonists (TPO) in treatment of idiopathic thrombocytopenia (ITP) allows avoiding immunosuppressive therapy.

Objective: Consumption analysis of TPO agonists at Hematology Clinic, University Clinical Center of Vojvodina and review of pharmacoeconomic aspect of these drugs.

Methods: A retrospective observational study included 25 patients with chronic ITP, treated with TPO agonists in period 2018–2024. Data on the prices of TPO agonists were obtained from ALIMIS Drug Consumption Register.

Results: In mentioned period, a total of 25 patients with chronic ITP were treated with TPO agonists. Out of total, 84% were initially treated with eltrombopag, and 16% with romiplostim. In 6 patients, eltrombopag was replaced by romiplostim (in three due to lack of response, and in three due to side effects). After 12 weeks 72% of patients achieved response, out of which 72% had $\geq 100 \times 10^9/L$, 22% ≥ 50 to $< 100 \times 10^9/L$ and 6% ≥ 30 to $< 50 \times 10^9/L$ platelets. The average length of treatment with TPO agonists was 9, and response after their discontinuation was 8 months. Two patients had an adverse reaction in the form of hepatotoxicity, while two had pronounced pain in bones and muscles, which was the reason for them to give up therapy. Average cost per treated patient for June 2024 was 1299.2 € for eltrombopag and 1560 € for romiplostim.

Conclusion: These drugs, in addition to their therapeutic effectiveness, represent a significant financial burden, which is why it is necessary to individualize the assessment of duration of treatment and moment of stopping therapy with TPO agonists.

Keywords: eltrombopag, romiplostim, TPO agonists

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THROMBOTIC THROMBOCYTOPENIC PURPURA IN A PATIENT WITH TAR SYNDROME

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SAŽETAK

Uvod: TAR (thrombocytopenia-absent radius) sindrom karakteriše bilateralno odsustvo radijusa i amegakariocitna trombocitopenija. Trombocitopenija može biti urođena ili se razviti u prvim mesecima života. Sindrom je udružen sa anomalijama skeleta, genitourinarnim i kardiovaskularnim malformacijama. TTP (trombotična trombocitopenijska purpura) predstavlja sindrom koji karakteriše stvaranje diseminovanih trombocitnih agregata u sitnim krvnim sudovima. Najčešće počinje akutno i u 75% pacijenata prisutna je trijada (trombocitopenija, mikroangiopatska hemolizna anemija, neurološki poremećaji). Za postavljanje dijagnoze pored standardnih laboratorijskih pretraga određuje se nivo ADAMTS13.

Prikaz slučaja: Pacijentkinja V.M. (19) kojoj je po rođenju dijagnostikovano TAR sindrom hospitalizovana je u Kliniku za hematologiju zbog trombocitopenije teškog stepena, anemije, hiperbilirubinemije i visokih vrednosti LDH. U urađenim laboratorijskim analizama dobili smo: Tr $2 \times 10^9/L$, Hgb 71 g/L, Rct 16,36%, Haptoglobin 0,1 g/L, LDH 1659 U/L, Coombs testovi negativni. Drugi dan hospitalnog lečenja komplikuje se oštećenjem govora po tipu disfazije i slabošću desne strane tela sa diskretnim desnostranim centralnim facijalisom. Nakon učinjenog CT endokranijuma registruje se intracerebralna hemoragija. Zbog sumnje na postojanje TTP određen je nivo ADAMTS13 – 0,2% što je sumnju potvrdilo. Lečenje je otpočeto kortikosteroidnom terapijom i svakodnevnom terapijskom izmenom plazme. Potom je nastavljeno sa 2 mg vinkristina ukupno tri doze, ali zbog neadekvatnog odgovora primenjen je Rixathon® (375 mg/m²) u jednoj dozi nedeljno tokom tri nedelje i postignuta je kompletna hematološka i neurološka remisija nakon 35 dana lečenja sa održavanjem trombocitopenije ranga $35-50 \times 10^9/L$.

Zaključak: Prikazali smo redak slučaj pacijentkinje sa TAR sindromom i TTP-om koji je pre svega bio dijagnostički izazov s obzirom na urođenu trombocitopeniju koju je pacijentkinja imala.

Ključne reči: TTP, ADAMTS13, TAR sindrom, trombocitopenija

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ABSTRACT

Introduction: TAR (Thrombocytopenia-absent radius) syndrome is characterized by the bilateral absence of radius and amegakaryocytic thrombocytopenia. Thrombocytopenia can be congenital or developed in the first months of life. The syndrome is associated with skeletal anomalies, genitourinary and cardiovascular malformations. TTP (thrombotic thrombocytopenic purpura) is a syndrome characterized by the formation of disseminated platelet aggregates in small blood vessels. Usually, it presents acutely and 75% of patients have triads (thrombocytopenia, microangiopathic haemolytic anaemia, neurological disorders). Diagnosis involves measuring ADAMTS13 levels in addition to standard laboratory tests.

Case report: Patient V.M. (19) diagnosed with TAR syndrome at birth was hospitalized at the Clinic for Hematology due to severe thrombocytopenia, anaemia, hyperbilirubinaemia and elevated LDH levels. Laboratory results showed: Tr $2 \times 10^9/L$, Hgb 71 g/L, Rct 16.36%, haptoglobin 0.1 g/L, LDH 1659 U/L, negative Coombs tests.

On the second day of hospitalization, V.M. developed dysphasia-type speech impairment and weakness on the right side of the body with mild right-sided central facialis. A CT scan revealed intracerebral hemorrhage. Suspecting TTP, the level of ADAMTS13 was determined – 0.2%, confirming the diagnosis.

Treatment began with corticosteroids and daily therapeutic plasma exchanges. Then, Vincristine (2 mg) was administered in three doses. Due to insufficient response, Rixathon® (375 mg/m²) was administered as a single dose weekly for three weeks. A complete hematological and neurological remission was achieved after 35 days of treatment with maintenance of platelet count $35-50 \times 10^9/L$.

Conclusion: This case highlights a rare instance of TAR syndrome complicated by TTP, a diagnostic challenge considering the patient's congenital thrombocytopenia.

Keywords: TTP, ADAMTS13, TAR syndrome, thrombocytopenia

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PROSEČNI VOLUMEN TROMBOCITA I ADIPONEKTIN: POTENCIJALNI MARKERI PROCENE TROMBOGENOG RIZIKA KOD PACIJENATA SA METABOLIČKIM SINDROMOM

MEAN PLATELET VOLUME AND ADIPONECTIN: POTENTIAL MARKERS OF THROMBOGENIC RISK IN PATIENTS WITH METABOLIC SYNDROME

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SAŽETAK

Uvod: Metabolički sindrom (MetSi) je značajno proinlatorsno i prokoagulantno stanje. Povezanost adiponektina, molekula sa značajnim antiinlatorsnim i antitrombogenim efektima, i njegova uloga u interakciji sa trombocitima i trombocitnim indeksima još uvek nije dovoljno istražena.

Cilj: Cilj našeg istraživanja bio je ispitati povezanost adiponektina sa brojem trombocita i trombocitnim indeksima kod pacijenata sa MetSi.

Metode: Istraživanje je sprovedeno kao studija preseka koja je uključila 113 ispitanika, 63 pacijenta sa dijagnozom MetSi i 50 zdravih kontrola sa jasnim kriterijumima za uključivanje i isključivanje. Dijagnoza MetSi je potvrđena u skladu sa definicijom IDF (The International Diabetes Federation). Za poređenje tri grupe korišćeni su statistički testovi ANOVA, Kruskal-Wallis i Man-Whitney test. Prilikom poređenja tri grupe, kako bi se smanjila greška α tipa, korišćena je Bonferroni korekcija sa značajnošću $p \leq 0,017$.

Rezultati: Eksperimentalna i kontrolna grupa nisu se razlikovale po polnoj i starosnoj distribuciji. Grupa pacijenata sa MetSi podeljena je u dve podgrupe prema odnosu trombociti-HDL holesterol (statistički cut-off od 220). Podgrupa sa većim odnosom bila je predijabetična (HbA1c 5,7%). Ista podgrupa pacijenata imala je značajno veće vrednosti prozapaljenjskih markera sa nižim HDL-om. U istoj podgrupi uočena je pozitivna povezanost između novoa adiponektina i prosečnog volumena trombocita (MPV).

Zaključak: Na osnovu naših rezultata, određivanje MPV-a i adiponektina može biti značajano u proceni kardiovaskularnog rizika kod pacijenata sa MetSi i predijabetesom, populaciji pacijenata koju karakteriše povećan rizik ka trombozi.

Ključne reči: adiponektin, trombociti, prosečna zapremina trombocita, metabolički sindrom

ABSTRACT

Introduction: Metabolic syndrome (MetSy) is a significant proinflammatory and procoagulant condition. The association of adiponectin, a molecule with significant anti-inflammatory and antithrombogenic effects, and its role in the interaction with platelets and platelet indices have not yet been sufficiently investigated.

Objective: We aimed to examine the association of adiponectin with platelet count and platelet indices in patients with MetSy.

Methods: The research was conducted as a cross-sectional study that included 113 subjects, 63 patients diagnosed with MetSy and 50 healthy controls, with clear inclusion and exclusion criteria. The diagnosis of MetSy was confirmed according to the definition of the IDF (The International Diabetes Federation). Statistical tests ANOVA, Kruskal-Wallis and Mann-Whitney test were used to compare the three groups. When comparing the three groups, in order to reduce the α -type error, the Bonferroni correction was used with a significance of $p \leq 0.017$.

Results: The experimental and control groups have similar gender and age distribution. The group of patients with MetSy was divided into two subgroups according to the platelet-HDL cholesterol ratio (statistical cut-off of 220). The subgroup with a higher ratio was prediabetic. The same subgroup had significantly higher values of pro-inflammatory markers with lower HDL and in this subgroup, a positive association between adiponectin and mean platelet volume (MPV) was observed.

Conclusion: Based on our results, the determination of MPV and adiponectin may be significant in the assessment of thrombogenic risk in patients with MetSy and prediabetes, a patient population characterized by an increased risk for thrombosis.

Keywords: adiponectin, platelets, mean platelet volume, metabolic syndrome

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ATYPICAL PRESENTATIONS OF THROMBOTIC THROMBOCYTOPENIC PURPURA – TWO CASE REPORTS

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SAŽETAK

Uvod: Trombozna trombocitopenična purpura (TTP) je potencijalno životno ugrožavajuća bolest, koja se obično klinički prezentuje neurološkom simptomatologijom i mikroangiopatskom hemoliznom anemijom (MAHA) i trombocitopenijom.

Cilj: Prikazati atipične slučajeve TTP-a, koji su se prezentovali izolovanom trombocitopenijom i/ili sa minimalnom MAHA.

Prikazi slučajeva: Prvi slučaj je muškarac 52 godine, hospitalizovan petog dana bolesti zbog slabosti i povišene temperature, a nakon potvrđene SARS-CoV2 infekcije i podatkom da je pre 16 godina imao tipičan atak TTP-a. U inicijalnoj krvnoj slici: Le 6,38x10⁹/L, Er 5,3 x10¹²/L, Hgb 159 g/L, Htc 0,5, Trci 7x10⁹/L. U razmazu periferne krvi retki shizociti, bilirubini 22,3/6,3 μmol/L, LDH 1501 U/L, haptoglobin < 0,08 g/L. Sedmog dana hospitalizacije dolazi do razvoja motorne afazije, uz sve znake MAHA, te je započeto sa terapijskim izmenama plazmi (TIP) i nakon pet je došlo do kompletne rezolucije. Drugi slučaj je žena 27 godina. Devet meseci nakon peripartalnog tipičnog ataka TTP-a je rehospitalizovana zbog novonastale disfazije i desnostrane hemipareze. U krvnoj slici bez anemije i trombocitopenije, u razmazu periferne krvi se na 1–3 vidna polja (uveličanje 100x) vide retki shizociti. S obzirom na prethodni atak TTP-a, a bez postojanja faktora rizika za cerebrovaskularni inzult, odmah je započeto sa TIP i nakon pet procedura uz drugu standardnu terapiju, dolazi do značajne regresije neuroloških ispada.

Zaključak: Kod bolesnika koji su imali tipični atak TTP-a treba posumnjati na relaps TTP-a i kod samo izolovane trombocitopenije, a u slučaju naglo nastale neurološke simptomatologije čak i u slučajevima bez trombocitopenije i MAHA.

Ključne reči: TTP, atipičan, MAHA

ABSTRACT

Introduction: Thrombotic thrombocytopenic purpura (TTP) is a potentially fatal disease that usually presents with neurological symptoms, microangiopathic hemolytic anemia (MAHA) and thrombocytopenia.

Objective: To report rare cases of TTP, characterised by isolated thrombocytopenia and/or minimal MAHA.

Case reports: Case 1. A 52-year-old male developed fever and malaise. Five days later he was hospitalized after the SARS-CoV2 infection confirmation with an information that he had experienced a typical episode of TTP 16 years earlier. Initial laboratory: WBC 6.38, RBC 5.3, HGB 159, HCT 0.5, PLT 7, bilirubin 22.3/6.3 μmol/L, LDH 1501 U/L, haptoglobin < 0.08 g/L. Rare schizocytes were found in the peripheral blood smear (PBS). Seven days following the admission, the patient developed motor aphasia and all the typical signs of MAHA. Therapeutic plasma exchange (TPE) was initiated. TPE was performed for five sessions, resulting in full recovery from the symptoms. Case 2. A 27-year-old female was rehospitalized due to new-onset dysphasia and right-sided hemiparesis nine months after the peripartal attack of typical TTP. There were no anemia or thrombocytopenia, with only a few schizocytes seen in PBS. Given the history of TTP attack and the absence of other cerebrovascular risk factors, TIP was initiated immediately. After undergoing five procedures along with standard therapy, there was a noticeable regression in neurological symptoms.

Conclusion: A previous history of TTP should prompt suspicion of relapse even in case of isolated thrombocytopenia. When it comes to sudden neurological symptoms, it should be suspected even in the absence of MAHA or thrombocytopenia.

Keywords: TTP, atypical, MAHA

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OSTALO

MISCELLANEOUS

UNIFOCAL LANGERHANS CELL HISTIOCYTOSIS: CASE REPORT

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SAŽETAK

Uvod: Histiocitoza Langerhansovih ćelija je heterogena grupa retkih idiopatskih poremećaja. Karakteristično je prisustvo tipičnih Langerhansovih ćelija (sa specifičnim imunofenotipskim profilom) i drugih hematopoetskih ćelija (T limfocita, makrofaga i eozinofila). Manifestacije, klinički tok, lečenje i ishod bolesti je veoma različit između pojedinih oblika Langerhansove histiocitoze.

Prikaz slučaja: Prikazujemo slučaj pacijenta, starog 37 godina, koji se u Urgentni centar javio zbog bolova u levoj strani grudnog koša. Nakon pregleda, standardne laboratorije i rendgenskog snimka grudnog koša nije utvrđen nijedan patološki nalaz. Bolovi su perzistirali i pacijent se nekoliko puta javljao na pregled u Urgentni centar. Nakon što je urađen CT pregled grudnog koša, opisane su osteolizne promene i mekotkivna solitarna promena na IV rebru. Zbog sumnje na plasmocitom upućen je hematologu. Nakon sprovedenog ispitivanja koje je potvrdilo da se radi o solitarnoj promeni, upućen je grudnom hirurgu. Urađena je resekcija dela IV rebra s leve strane. Patohistološki i imunohistohemijski nalaz ukazao je na tipičan nalaz za histiocitozu Langerhansovih ćelija (CD1a +, S100+, ostali urađeni markeri negativni, Ki67 < 5%). Urađen je PET sken čitavog tela koji nije ukazao na nakupljanje radiofarmaka u nešto uvećanoj jetri i slezini. Ovakav nalaz doprineo je da se ovaj pacijent shvati kao unifokalna histiocitoza Langerhansovih ćelija, što ne zahteva dopunsku hemioterapiju. Pacijent se trenutno dobro oseća, nema tegoba.

Zaključak: Prikaz ovog slučaja ukazuje na veliku heterogenost ove grupe obojenja, njihovo nedovoljno poznavanje i klinički značaj unifokalne infiltracije, te postavlja pitanje da li je dovoljno uraditi samo radiološku dijagnostiku ili je neophodno uraditi i biopsije organa sumnjivih na infiltraciju.

Ključne reči: histiocitoza Langerhansovih ćelija, unifokalni oblik, prikaz slučaja

ABSTRACT

Introduction: Langerhans cell histiocytosis is heterogenous group of rare, idiopathic disorders characterised with the presence of typical Langerhans cells (with specific immunophenotype) and other haematopoietic cells (T lymphocytes, macrophages and eosinophils). Manifestations, clinical courses, treatment and prognosis are very different between different subgroups of the disorder.

Case report: We present the case, of the patient, 37 years old, who was visiting Emergency room of our hospital, due to constant pains in the left side of the chest. After examinations, standard laboratory testing and chest X ray there were no pathological findings. Due to persistent pains CT scan of the chest was performed and it revealed osteolytic lesions and tumor infiltration of the IV rib, on the left side of the chest. He was directed to haematologist, as suspected solitary plasmocytoma. After comprehensive resection of the fourth rib, pathohistological and immunophenotypic finding was typical for the Langerhans cell histiocytosis (CD1a +, S100 +, other markers were negative and Ki67 was < 5 %). PET scan was performed and the finding did not show any signs of the radiopharmaceutical accumulation in enlarged liver and spleen. This finding was indicating that it was the case of the unifocal Langerhans cell histiocytosis. Patient is, now, without any symptom and in the very good condition.

Conclusion: This case report indicates great heterogeneity of this disorder, insufficient knowledge of the clinical importance of the unifocal infiltration and rises question whether is enough to perform only radiological diagnostic or is it necessary to perform biopsy of the suspected organs.

Keywords: Langerhans cell histiocytosis, unifocal, case report

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THE INFLUENCE OF THE THIRD AND FOURTH GENERATION OF COMBINED ORAL CONTRACEPTIVES ON HEMATOLOGICAL AND HEMOSTASIS PARAMETERS

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SAŽETAK

Uvod: Oralni kontraceptivi predstavljaju efikasni vid kontrole plodnosti sa brojnim potencijalnim neželjenim efektima.

Cilj: Cilj rada je praćenje razlike vrednosti hematoloških i hemostaznih parametara kod žena koje su uzimale oralne kontraceptive i onih koje nisu.

Metode: Deskriptivna studija je obuhvatila ukupno 121 ispitanica, klasifikovanih u grupu od 72 ispitanice koje su upotrebljavale oralne kontraceptive i grupu od 49 ispitanica bez terapije.

Rezultati: Između ispitivane i kontrolne grupe nije bilo razlike u polu, starosti, i indeksu telesne mase. Učestalost pušenja je bila veća kod kontrolne grupe (36% vs. 19%; $\chi^2 = 0,039$). Nije bilo statički signifikantne razlike u broju leukocita sa diferencijalnom krvnom slikom, koncentracije hemoglobina, hematokrita, broja eritrocita i eritrocitnih parametara (MCV, MCH, MCHC) između grupa. Postotak retikulinskih trombocita je bio veći u ispitivanoj grupi, ali bez statistički značajne razlike. Odnos broja trombocita i limfocita je bio veći u kontrolnoj, ali bez statistički značajne razlike, dok u odnosu neutrofila i limfocita nije bilo razlike među grupama. Aktivisano parcijalno trombolastinsko vreme (aPTT) i protrombinsko vreme (PT) je bilo statistički značajno kraće u ispitivanoj grupi ($24,69 \pm 1,83$ sec. vs. $25,78 \pm 2,85$ sec.; $p = 0,011$) i ($9,72 \pm 2,16$ sec. vs. $10,50 \pm 1,93$ sec.; $p = 0,045$). Vrednosti fibrinogena i d-dimera se nisu razlikovale, dok su vrednosti antitrombina i von Willebrandovog faktora bile niže u ispitivanoj grupi, ali bez statistički značajne razlike.

Zaključak: Povišen rizik od nastanka venskog tromboembolizma je povezan sa upotrebom kombinovanih oralnih kontraceptiva povećavanjem koagulabilnost krvi.

Ključne reči: kombinovana oralna kontracepcija, venski tromboembolizam, hemostaza

ABSTRACT

Introduction: Oral contraceptives represent an effective form of fertility control, with numerous potential side effects.

Objective: The aim was to monitor the difference in hematological and hemostatic parameters in users and non-users of oral contraceptive therapy.

Methods: A descriptive study included 121 subjects, classified as 72 oral contraceptive users and 49 non-users.

Results: There was no difference in sex, age, and body mass index between the groups. The frequency of smoking was higher in non-users compared to users (36% vs. 19%; $\chi^2 = 0.039$). There was no significant difference in the number of leukocytes, parameters of the differential white blood picture, hemoglobin concentration, hematocrit, number of erythrocytes, and erythrocyte parameters (MCV, MCH, MCHC) when comparing the groups. The percentage of reticulated platelets was higher among users, without a statistically significant difference. The platelets to lymphocytes ratio was higher among users, without significant difference, while there was no difference in the neutrophils to lymphocytes ratio. Activated partial thromboplastin time (aPTT) and prothrombin time (PT) were significantly shorter in the users compared to non-users (24.69 ± 1.83 sec. vs. 25.78 ± 2.85 sec.; $p = 0.011$) and (9.72 ± 2.16 sec. vs. 10.50 ± 1.93 sec.; $p = 0.045$), respectively. There was no difference in fibrinogen and d-dimer concentrations, while antithrombin and von Willebrand factor were lower in the control group, without statistical significance.

Conclusion: The use of oral contraceptives of the third and fourth generation leads to changes in the hemostasis functionality in terms of the shortening of aPTT and PT, thus potentially influencing the venous thrombosis risk.

Keywords: combined oral contraceptives, venous thromboembolism, hemostasis

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DEVELOPMENT OF FEBRILE NEUTROPENIA IN PATIENTS WITH HEMATOLOGICAL
MALIGNANCIES TREATED IN DAILY CARE UNIT OF TERTIARY INSTITUTION

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SAŽETAK

Uvod: Neutropenija uzrokovana primenom hemioterapije (HT) često se komplikuje pojavom febrilne neutropenije (FN), koja je povezana sa razvojem infekcija, redukcijom doze leka/odlaganjem HT, narušenim kvalitetom života i povećanim troškovima lečenja.

Cilj: Ispitivanje povezanosti faktora rizika za razvoj FN i primena G-CSF kod hematoških bolesnika.

Metode: Obuhvaćeno je 90 bolesnika sa dijagnozom limfoma, multiplog mijeloma-MM i mijelodisplaznog sindroma-MDS lečenih u Dnevnoj bolnici, Klinike za hematologiju, UKCS od januara do juna 2024.

Rezultati: FN su bile češće kod muškaraca (59,1%; $p = 0,065$), bolesnika sa višim ANC pre HT (4,57 vs. 3,71; $p = 0,03$), prethodnim infekcijama (22,7% vs. 8,8%; $p = 0,064$), višim vredostima CRP-a (25,1 vs. 10,2; $p = 0,004$) i više primenjenih HT linija ($p < 0,001$) sa sledećom distribucijom: ≥ 3 terapijske linije (36,4%, vs. 10,3%; $p = 0,004$); ≥ 10 ciklusa HT (40,9% vs. 17,6%; $p = 0,025$) ili imunoterapije (31,6% vs. 11,3%; $p = 0,042$). Pojava FN pozitivno je korelirala sa gradusom neutropenije ($p \leq 0,001$), kliničkim stadijumom bolesti i sa bulky tumorskom masom (54,5% vs. 25%; $p = 0,01$). Uočena je negativna korelacija sa ECOG performans statusom. Distribucija učestalosti FN: NHL (77,3%), MDS (15%) i MM (11%). Distribucija FN prema tipu limfoma: 57,9% kod agresivnih, 31,6% kod indolentnih i 10,5% kod Hodgkinovog limfoma. Bolesnici sa FN su imali češće infekcije (59,1% vs. 27,9%; $p = 0,008$), primenu antibiotika (95,5% vs. 33,3%; $p < 0,001$), primenu G-CSF (54,1% vs. 11,8%; $p < 0,001$) kao i veći broj primenjenih ampula G-CSF ($p = 0,002$).

Zaključak: Naša studija je pokazala da je na razvoj FN uticao veći broj terapijskih linija kao i ciklusa imunohemioterapije, klinički stadijum bolesti, bulky tumorska masa i stepen agresivnosti limfoma, dok ANC nije bio povezan sa razvojem FN.

Ključne reči: febrilna neutropenija, G-CSF, hematološki maligniteti

ABSTRACT

Introduction: Chemotherapy-induced neutropenia is often complicated by development of febrile neutropenia (FN) which is related to infections, dose reductions/delay of chemotherapy, quality of life deterioration and increased treatment costs.

Objective: To research connection between risk factors for FN and usage of G-CSF in hematological patients.

Methods: We evaluated 90 patients with lymphoma, multiple myeloma and myelodysplastic syndrome treated in Daily care Unit of hematology, UCCS in period January-Jun 2024.

Results: FN was more common in male (59.1%; $p = 0.065$), patients with bigger initial ANC (4.57 vs. 3.71; $p = 0.03$), previous infections (22.7% vs. 8.8%; $p = 0.064$), bigger CRP (25.1 vs. 10.2; $p = 0.004$) and more chemotherapy lines ($p < 0.001$) with following distribution: ≥ 3 therapy lines (36.4%, vs. 10.3%; $p = 0.004$); ≥ 10 cycles of chemotherapy (40.9% vs. 17.6%; $p = 0.025$) or immunotherapy (31.6% vs. 11.3%; $p = 0.042$). The development of FN correlated positively with grade of neutropenia ($p \leq 0.001$), clinical stage and bulky tumor (54.5% vs. 25%; $p = 0.01$) but correlated negatively with ECOG performance status. Frequency of following diagnosis was: NHL (77.3%), MDS (15%) i MM (11%). Frequency of following lymphoma types was: 57.9% aggressive, 31.6% indolent and 10.5% Hodgkin lymphoma. Patients with FN had more frequent infections (59.1% vs. 27.9%; $p = 0.008$), administration of antibiotics (95.5% vs. 33.3%; $p < 0.001$) and G-CSF (54.1% vs. 11.8%; $p < 0.001$) and greater number of applied ampoules of G-CSF ($p = 0.002$).

Conclusion: Our study shown that number of therapy lines or cycles of immunochemotherapy, clinical stage, bulky tumor and aggressiveness of lymphoma did affect on development of FN contrary to ANC which had no effect.

Keywords: febrile neutropenia, G-CSF, hematological malignancies

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OVERALL SURVIVIOR AND BACTERIAL INFECTION RISK IN PATIENTS WITH SEVERE NEUTROPENIA AND MYELODISPLASTIC SYNDROME

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SAŽETAK

Uvod: Mijelodisplastični sindrom (MDS) se karakteriše jednolinijskom ili višelinij-skom displazijom i citopenijom u perifernoj krvi. Kod bolesnika sa MDS najčešća inicijalna manifestacija je anemija, a znatno ređe se ispoljava teškom neutropenijom (TN).

Cilj: Cilj ove studije bio je utvrditi incidencu bakterijskih infekcija kod pacijenata sa MDS i TN.

Metode: U ovoj studiji retrospektivno su pregledani bolesnici koji su lečeni u KBC „Dr Dragiša Mišović – Dedinje“, sa MDS i TN kao početnom manifestacijom (ANC < 500/ul). Analizirani su izveštaji 168 bolesnika sa MDS od kojih je 11 (6,5%) imalo TN kao inicijalnu prezentaciju. Bolesnici su kategorisani prema Fab klasifikaciji i R-IPSS. Kumulativna incidenca infekcija je izračunata prema Kaplan-Majeru.

Rezultati: Infekcije su potvrđene kod 9 bolesnika sa MDS i TN tokom prvih 6 meseci od postavljanja dijagnoze. Hemokulture su bile pozitivne na bakterije (*Staphylococcus aureus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*) kod 5 bolesnika (55%), urinokulture (*E. coli*) kod 3 (27%) i 1 bolesnik je imao gljivičnu infekciju (9%). Kumulativna incidenca infekcija bila je 47% tokom prvih 6 meseci i 44% u prvoj godini. Univarijantnom analizom faktora identifikovani su: broj neutrofila niži od 500/ul kao vremenski zavisna kovarijanta, muški pol i RAEB/RAEBt u odnosu na RA; kao faktori koji su značajno povezani sa incidencom infekcija. Bolesnici sa TN i MDS su imali značajno kraće preživljavanje (21 mesec) u odnosu na bolesnike sa višim brojem neutrofila (62 meseca).

Zaključak: Na osnovu ovih podataka možemo zaključiti da je izrazito snižen broj neutrofila povezan sa većom incidencom infekcija i kraćim preživljavanjem bolesnika sa MDS, nezavisno od godina i R-IPSS.

Gljučne reči: teška neutropenija, mijelodisplastični sindrom, infekcije, preživljavanje

ABSTRACT

Introduction: Myelodysplastic syndrome (MDS) is characterized by single or multiple lineage dysplasia and peripheral cytopenia. MDS patients are most frequently presented with variable degree anemia, but occasionally MDS could be manifest with severe neutropenia (SN).

Objective: Aim of this study was to determine the incidence of infection in patients with SN and MDS.

Methods: In this study, we retrospectively revised the patients with SN as the initial presentation of MDS that were treated in UHC “Dr. Dragisa Misovic – Dedinje”. We analyzed 168 patients with MDS, 11 patients (6,5%) experienced SN as early event. Patients with MDS were classified according to the Fab classification and the R-IPSS. The cumulative incidence of infections event was calculated using Kaplan-Meier.

Results: Infections were confirmed in 9 patients with SN and MDS in the first 6 months after a new diagnose. Infection events included blood culture positivity for common pathogens (*Staphylococcus aureus*, *Enterococcus faecalis*, *Klebsiella pneumoniae*) in 5 patients (55%), urine culture (*E. coli*) in 3 patients (27%) and 1 patient (9%) was with fungal event. The cumulative incidence of infection was 47% at 6 months and 44% at 1 year. In univariate analysis of factors that included a neutrophil count of less than 500/ul as a time-dependent covariate, male sex, RAEB/RAEB-t against RA significantly influenced the incidence of IE. Patients with SN and MDS had shorter overall survivor (21 months) compared to patients with higher neutrophil count (62 months).

Conclusion: SN was associated with higher incident of infection and shorter overall survivor of patients with MDS.

Keywords: severe neutropenia, myelodysplastic syndrome, infections, overall survivor

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HAEMATOLOGICAL TOXICITIES OF CDK4/6 INHIBITORS IN METASTATIC BREAST CANCER, SINGLE INSTITUTION EXPERIENCE

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SAŽETAK

Uvod: Hematološke toksičnosti predstavljaju najčešće neželjeno dejstvo primene CDK4/6 inhibitora (CDK4/6i). Zbog novine ovih lekova, postoji generalna potreba za dodatnim podacima koji bi identifikovali potencijalne predisponirajuće faktore za razvoj hematoloških toksičnosti.

Cilj: Ova studija ima za cilj da prikaže naša iskustva o primeni ribocicliba i palbocicliba u ovom kontekstu.

Metode: U ovoj retrospektivnoj deskriptivnoj studiji, ispitivali smo primenu CDK4/6i kod pacijenata sa metastatskim karcinomom dojke, lečenih na Odeljenju dojke IORSa u periodu od 1.1.2021. do 1.6.2024.

Rezultati: U studiju je uključeno 128 pacijenata, 43% bilo je na terapiji palbociclibom, a 57% ribociclibom. Medijana starosti bila je 60 godina (opseg 30–83). Medijana praćenja iznosila je 12 meseci (opseg 2–23). Neutropenija je uočena kod 82,1% (gradus 3/4: 43%) pacijenata. Redukcija doze zbog ponavljanih neutropenija gradusa 3/4 bila je potrebna kod 21,1% ispitanika. Anemije i trombocitopenije gradusa 3/4 primećene su kod 0,8% i 1,6% pacijenata. Obustava terapije zbog hematoloških toksičnosti bila je neophodna kod 2 pacijenta (1,5%). Nije bilo statistički značajne razlike između dva leka kada je upitanju u incidenca hematološke toksičnosti ($p = 0,443$). Prethodna primena hemioterapije u metastatskoj fazi bolesti, nije bila povezana sa učestalošću hematološke toksičnosti ($p = 0,565$). Palijativna radioterapija kostiju pokazala je statistički značajnu povezanost sa potrebom za redukcijom doze CDK4/6i ($p = 0,001$, $r = 2,83$). Medijana preživljavanja bez progresije bolesti (PFS) nije dostignuta, ali nije postojao trend koji bi ukazivao da redukcija doze CDK4/6i utiče na PFS ($p = 0,719$).

Zaključak: Većina pacijenata tretiranih CDK4/6i razvija neutropeniju, ali su obustave terapije retke. Palijativna radioterapija kostiju je povezana sa češćom doznom redukcijom CDK4/6i, ali redukcija doze ovih lekova nije uticala na preživljavanje.

Ključne reči: metastatski karcinom dojke, CDK4/6 inhibitori, hematološka toksičnost

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ABSTRACT

Introduction: Haematological adverse events (AE) represent the most common toxicities associated with use of CDK4/6 inhibitors (CDK4/6i). However, data regarding predisposing factors that could lead to haematological AEs is in demand.

Objective: This study aims to present our experience regarding the use of ribociclib and palbociclib in this context.

Methods: In this retrospective-descriptive study, we investigated use of CDK4/6i in patients with metastatic breast cancer, treated at our Medical Oncology Department, between 1.1.2021 and 1.6.2024.

Results: This study included 128 patients, 43% received palbociclib, 57% received ribociclib. Median age was 60 (range 30–83). Median follow-up was 12 months (range 2–34). Neutropenia was observed in 82.1% (grade 3/4: 43%) of patients. Dose reductions were necessary in 21.1% of patients due to repeated grade 3/4 neutropenia's. Grade 3/4 anaemia and thrombocytopenia were recorded in 0.8% and 1.6% of patients. Therapy was discontinued twice (1.5%) due to haematological AEs. No statistical difference was observed between two drugs in regard to incidence of haematological AEs ($p = 0.443$). Previous treatment with chemotherapy in metastatic setting was not associated with haematological toxicities ($p = 0.565$). Palliative bone radiotherapy (39.8% of patients) had shown statistical correlation with dose reductions of therapy ($p = 0.001$, $r = 2.83$). Median progression free survival (PFS) was not reached, but there was no trend indicating that dose reductions of CDK4/6i would impact PFS ($p = 0.719$).

Conclusion: Majority of patients treated with CDK4/6i develop neutropenia, but discontinuations of therapy are rare. Palliative bone RT was associated with increased need for dose reductions of CDK4/6i, but dose reductions of therapy did not negatively impact survival outcomes.

Keywords: metastatic breast cancer, CDK4/6 inhibitors, haematological toxicity

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SPLENOMEGALY AS A DIAGNOSTIC CHALLENGE: CASE REPORT

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SAŽETAK

Uvod: Splenomegalija može biti znak brojnih oboljenja, pa je tokom obrade pacijenta sa uvećanom slezinom potrebno uzeti u obzir infektološke, imunološke, hematološke uzroke, oboljenja jetre i portnog krvotoka, kao i bolesti odlaganja.

Cilj: Prikazati pacijenta sa masivnom splenomegalijom i put do postavljanja definitivne dijagnoze.

Prikaz slučaja: Muškarac, starosti 26 godina, javlja se hematologu sa simptomima malaksalosti i nelagodnosti pod lijevim rebarnim lukom. Laboratorijske analize otkrivaju pancitopeniju (Er 3,9, Hgb 98, Leu 1,9, Tr 41), dok je radiološkom obradom uočena masivna splenomegalija (30 cm), umjerena hepatomegalija sa znacima portne hipertenzije i aksilarna limfadenopatija. Mikrobiološkim i imunološkim analizama isključeni su infektivni i imunološki uzroci. Gastroenterološkom obradom eliminisana je dijagnoza ciroze i mogući necirotični uzroci portne hipertenzije. Gornja i donja endoskopija su bile uredne. Biopsija koštane srži i aksilarnog limfnog čvora nisu ukazale na primarnu hematološku bolest. PET CT otkriva povećano preuzimanje radiofarmaka cervikalno, aksilarno, paraortokavalno, ilijačno (SUV Max 3,0), i u slezini (SUV max 5,1). Urađena je dijagnostička splenektomija, PH analiza ukazala je na hiperemiju slezinske vaskulature. Zaključeno je da se radi o idiopatskoj necirotičnoj portnoj hipertenziji (Banti sindrom) sa posljedičnom kongestivnom splenomegalijom. U pitanju je rijetko oboljenje koje se karakteriše hroničnom kongestijom slezine, splenomegalijom i portnom hipertenzijom bez prisustva ciroze jetre. Etiologija nije razjašnjena, najverovatnije se radi abnormalnostima u portnoj mikrocirkulaciji. Splenektomija je dovela do regulacije hemograma uz blagu trombocitozu, te se naš pacijent nastavlja pratiti.

Zaključak: Diferencijalna dijagnoza splenomegalije je često složena i zahtijeva opsežnu dijagnostiku i multidisciplinarnu pristup.

Gljučne reči: splenomegalija, diferencijalna dijagnoza, idiopatska necirotična portna hipertenzija, splenektomija

ABSTRACT

Introduction: Splenomegaly can indicate various diseases, necessitating consideration of infectious, immunological, hematological causes, liver diseases, portal circulation disorders, and storage diseases during evaluation.

Objective: To present a case of massive splenomegaly and the pathway to a definitive diagnosis.

Case report: A 26-year-old man presented with fatigue and discomfort under the left costal arch. Laboratory analyses revealed pancytopenia (Er 3.9, Hgb 98, Leu 1.9, Tr 41). Radiological imaging showed massive splenomegaly (30 cm), moderate hepatomegaly with signs of portal hypertension, and axillary lymphadenopathy. Microbiological and immunological analyses excluded infectious and immunological causes. Gastroenterological evaluation ruled out cirrhosis and non-cirrhotic causes of portal hypertension. Upper and lower endoscopies were normal. Bone marrow and axillary lymph node biopsies did not indicate primary hematological disease. PET CT showed increased uptake in cervical, axillary, para-aortocaval, and iliac regions (SUV Max 3.0) and in the spleen (SUV Max 5.1). Diagnostic splenectomy was performed, revealing hyperemia of the splenic vasculature. The diagnosis was idiopathic non-cirrhotic portal hypertension (Banti's syndrome) with congestive splenomegaly. This rare condition is characterized by chronic congestion of the spleen, splenomegaly, and portal hypertension without liver cirrhosis. The etiology is unclear, most likely related to abnormalities in portal microcirculation. Post-splenectomy, the patient's blood count normalized with mild thrombocytosis, and he continues to be monitored.

Conclusion: The differential diagnosis of splenomegaly is complex, requiring extensive diagnostics and a multidisciplinary approach.

Keywords: splenomegaly, differential diagnosis, idiopathic non-cirrhotic portal hypertension, splenectomy

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TREATMENT OF FETAL ANEMIA IN ALLOIMMUNIZED PREGNANT WOMEN

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SAŽETAK

Uvod: Aloimunizaciju trudnica pokreću nepodudarni krvnogrupsni antigeni na eritrocitima fetusa, nasleđeni od oca. Prođukovana antieritrocitna antitela prolaze hematoplacentnu barijeru i hemoliziraju eritrocite fetusa, uzrokujući anemiju. Najtežu izazivaju antigeni D, c (krvnogrupsni sistem Rhesus) i K (Kell). Hemoliznu bolest fetusa/novorođenčeta (HBFN) karakterišu teška anemija, hiperbilirubinemija i kernikterus. Ultrasonografsko merenje brzine protoka u srednjoj cerebralnoj arteriji fetusa otkriva anemiju. Terapija je intrauterina transfuzija (IUT).

Cilj: Prikaz naših rezultata od 2018. do 2023. godine – IUT i ishod trudnoća.

Metode: Trudnicama je praćen skrining, identifikacija i titar antieritrocitnih antitela. Iz pupčanika je određena krvna grupa i direktni antiglobulinski test; kompletna krvna slika – pre i nakon IUT.

Rezultati: IUT je primenjena kod 26 trudnica; ukupno 74 (3 intraperitonealne i 71 intravaskularne). 7 fetusa je imalo blagu anemiju, 16 srednje tešku a 3 tešku anemiju (hidrops). Najveći početni titar anti-D antitela bio je 2048, najniži 64. Medijana IUT je 3 po fetusu, (1 do 7). Srednja gestacijska starost kod prve IUT bila je 29 ng, (od 16–37 ng). Hematokrit jedinica eritrocita za IUT: 0,69–0,80. Prime-njeni volumen eritrocita po proceduri bio je od 20–135 ml. Srednja početna vrednost Hb fetusa bila je 78 g/L, Ht 0,24, Tr $204 \times 10^9/L$. Posle IUT srednja vrednost Hb bila je 114 g/L, Ht 0,35, Tr $181 \times 10^9/L$. Perinatalni ishod: 22 zdrava novorođenčeta; 4 sa anemijom koja je zahtevala transfuziju posle rođenja. Medijana Hb posle rođenja bila je 141 g/L, medijana Ht 0,39.

Zaključak: IUT je bezbedna invazivna metoda, obezbeđuje preživljavanje fetusa. Aloimunizovane trudnice treba uputiti u specijalizovanu ginekološku ustanovu pre nastanka hidropsa fetusa.

Cljučne reči: fetalna anemija, intrauterina transfuzija, aloimunizacija

ABSTRACT

Introduction: Alloimmunization in pregnant women are triggered by mismatched antigens on the erythrocytes of the fetus, inherited from the father. Produced red cell antibodies cross the hematoplacental barrier and hemolyze fetal erythrocytes, causing fetal anemia. Hemolytic disease of the fetus/newborn (HBFN) is characterized by hyperbilirubinemia and kernicterus in addition to untreated severe anemia. Ultrasonographic measurement of fetal middle cerebral artery flow velocity reveals anemia. The therapy is intrauterine transfusion (IUT).

Objective: Presentation of our results in the period from 2018 to 2023 – IUTs and the outcomes.

Methods: Pregnant women were monitored for screening, identification and titer of erythrocytes antibodies. Blood group and DAT were determined from the fetal cord blood; blood test result – before and after IUT.

Results: IUT was used in 26 fetuses; a total of 74 (3 intraperitoneal and 71 intravascular transfusions). 7 fetuses had mild, 16 moderate and 3 severe anemia. The median IUT was 3 per fetus (1–7). The mean gestational age at the application of the first IUT was 29 ng (16–37). The applied volume of erythrocytes in the procedure was 20–135 ml. Mean fetal Hb before IUT was 78 g/L, Ht 0,24, Tr $204 \times 10^9/L$. After IUT the mean Hb was 114 g/L, Ht 0,35, Tr $181 \times 10^9/L$. Perinatal outcome: 22 healthy newborns, 4 with anemia that required transfusion. Median Hb after birth was 141 g/L, median Ht was 0,39.

Conclusion: IUT is a safe, invasive method. Alloimmunized pregnant women should be referred to a specialized gynecological obstetric institution before the development of fetal hydrops.

Keywords: fetal anemia, intrauterine transfusion, alloimmunization

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MEGALOBlastic ANAEMIA AS PART OF THE AUTOIMMUNE POLYGLANDULAR SYNDROME TYPE II (SCHMIDT SYNDROME)

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SAŽETAK

Uvod: Megaloblastna anemija može biti udružena sa drugim autoimunskim manifestacijama, te predstavljati samo jednu od komponenti mnogo kompleksnijeg poremećaja. Šmitov sindrom ili autoimuni poliglandularni sindrom tipa II je autoimuni poremećaj koji se karakteriše kombinacijom adrenalne insuficijencije, autoimunog hipotireoidizma i šećerne bolesti. Druge autoimunske manifestacije takođe se sreću u sklopu ovog sindroma.

Cilj: Prikaz kliničkog toka bolesnice sa Šmitovim sindromom.

Prikaz slučaja: Prezentujemo slučaj bolesnice Đ. K. starosti 58 godina, koja je inicijalno primljena u jedinicu intenzivnog lečenja naše ustanove u teškom stanju sa znacima akutne nadbubrežne insuficijencije, a tokom hospitalizacije je konsultovan hematolog i postavljena je dijagnoza perniciozne anemije, uz ranije utvrđene komorbiditete u vidu insulin zavisne šećerne bolesti i hipotireoidizma. Utvrđeno je da bolesnica ispunjava uslove za postavljanje dijagnoze autoimunog poliglandularnog sindroma tip II (Schmidt syndrome). Nakon inicijalnog zbrinjavanja u našoj ustanovi, stabilizacije opšteg stanja i korekcije elektrolitskog i metaboličkog disbalansa bolesnica je premeštena u Univerzitetski klinički centar Novi Sad, na Kliniku za endokrinologiju i bolesti metabolizma, gde je pored već ranije uvedene supstitucione parenteralne terapije vitamina B12, L-tiroksina uvedena i supstituciona terapija parenteralnim, a potom oralnim glikokortikoidom, kao i peroralnim mineralokortikoidom.

Zaključak: U slučaju da postavljene dijagnoze perniciozne anemije, potrebno je tragati i za drugim autoimunskim oboljenjima koja mogu biti udružena sa istom, a koja mogu potencijalno i ugroziti život bolesnika.

Ključne reči: Šmitov sindrom, megaloblastna anemija, nadbubrežna insuficijencija

ABSTRACT

Introduction: Megaloblastic anaemia can be combined with other autoimmune manifestations, and be only one the components of a significantly more severe disorder. Schmidt syndrome, or autoimmune polyglandular syndrome type II, is an autoimmune disorder which is characterized by a combination of adrenal insufficiency, autoimmune hypothyroidism and diabetes mellitus. Other autoimmune manifestations may also be present as part of this syndrome.

Objective: Presentation of the clinical course of a patient with Schmidt syndrome.

Case report: We are presenting the case of patient Đ. K., age 58, who was admitted to the intensive care unit in a severe condition with signs of acute adrenal insufficiency, and during hospitalization, a haematologist was consulted, and the patient was diagnosed with pernicious anaemia, with previously established comorbidities in the form of insulin dependent diabetes mellitus and hypothyroidism. It was soon established that the patient fulfilled the conditions for being diagnosed with autoimmune polyglandular syndrome type II (Schmidt syndrome). After initial treatment, the stabilization and correction of the electrolytic and metabolic imbalance, the patient was transferred to the University Clinical Centre of Novi Sad, in the endocrinology diseases clinic. In addition to the previously introduced parenteral vitamin B12 therapy, L-thyroxine, a substitution therapy was introduced, initially using parenteral and later oral glucocorticoid, as well as peroral mineralocorticoid.

Conclusion: In the case of diagnosis of pernicious anaemia, other autoimmune diseases should be considered which may be combined with the previously mentioned one, and potentially be life-threatening for the patient.

Keywords: Schmidt syndrome, megaloblastic anaemia, adrenal insufficiency

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ASSOCIATION OF MONOCLONAL GAMMOPATHY WITH HEMATOLOGICAL MALIGNANCIES

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SAŽETAK

Uvod: Udruženost monoklonske gamapatije (MG) i limfoidnih neoplazmi (LN) je dobro poznata.

Cilj: rada je da se utvrdi povezanost MG sa određenim tipovima limfoidnih i mijeloidnih neoplazmi (MN), kao i da se utvrdi da li postoji statistički značajna razlika između ove dve grupe bolesnika u odnosu na pol, starost, kao i tip i nivo M komponente.

Metode: Retrospektivno su analizirani nalazi imunofiksacije seruma/urina rađeni u UKC Vojvodine od 2017–2022. godine. Kod 37 od 164 ispitanika, kod kojih je prvi put rađena imunofiksacija, je detektovana MG udružena sa hematološkim malignitetom (osim multiplog mijeloma).

Rezultati: Bilo je 23 žene i 14 muškaraca, medijane starosti 66 godina. Od ukupnog broja bolesnika 81% je imao udruženu LN, dok je 19% bolesnika imalo udruženu MN. Od LN najčešća je bila Waldenströмова makroglobulinemija (33%), potom slede HLL i MZL (16,6%), kao i DKBL i FL (po 10%), mantle cell limfom i limfoplazmocitni limfom (po 6,6%). Od MN tri bolesnika je imalo MPN, dva bolesnika MDS, dok su dve bolesnice imale leukemije (HMMoL i AML). Dve trećine bolesnika je imalo udruženu IgM paraproteinemiju. MN su bile povezane uglavnom sa IgG, dok je većina LN bila povezana sa IgM paraproteinom. Osim tipa paraproteina, nije bilo statistički značajne razlike između LN i MN udruženih sa MG, ako se posmatra pol, starost i nivo M komponente.

Zaključak: Osim sa limfoidnim neoplazmama, MG može biti povezana i sa mijeloidnim neoplazmama. Dok su LN uglavnom povezane sa IgM paraproteinom, MN su povezane sa IgG.

Ključne reči: monoklonska gamapatija, malignitet, mijeloidna neoplazma, limfoidna neoplazma

ABSTRACT

Introduction: The association of monoclonal gammopathy (MG) with lymphoid neoplasms (LN) is a well-known fact.

Objective: To investigate the relationship between MG and various types of lymphoid and myeloid neoplasms (MN); to determine if there are significant differences between these two groups in terms of gender, age, type and level of M component.

Methods: The results of serum/urine immunofixation tests conducted at the UCC of Vojvodina from 2017 to 2022 were retrospectively analyzed. Out of 164 patients, in whom immunofixation was performed for the first time, 37 patients with MG associated with hematological malignancies (excluding multiple myeloma) were included in this study.

Results: There were 23 women/14 men with the median age 66. Eighty-one percent of patients had MG associated with LN, while 19% had associated MN. Among the LNs, Waldenström's macroglobulinemia was the most common (33%), followed by CLL and MZL (16.6% each), as well as DLBCL and follicular lymphoma (10% each), mantle cell lymphoma and lymphoplasmacytic lymphoma (6.6% each). As for MNs, three patients had MPN, two had MDS, while two had leukemias (CMMoL and AML). Two thirds of patients had IgM paraproteinemia. MNs were primarily associated with IgG paraprotein, while most LNs were associated with IgM. Apart from the type of paraprotein, there were no statistically significant differences between the two groups regarding sex, age and M component level.

Conclusion: MG can be associated with both LN and MN. While LNs are predominantly associated with IgM paraprotein, MNs are more often associated with IgG.

Keywords: monoclonal gammopathy, malignancy, myeloid neoplasm, lymphoid neoplasm

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THERAPY OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

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SAŽETAK

Uvod: Paroksizmalna noćna hemoglobinurija (PNH) je retka stečena klonska bolest matične hematopetske ćelije koja nastaje zbog somatske mutacije gena *pigA*, koji utiče na sintezu glikozilfosfatidilinozitola (GPI) i dovodi do delimičnog ili potpunog nedostatka beločevina CD59 (membranskog inhibitora reaktivne lize) i CD55 (faktora ubrzane razgradnje) pa su ćelije preosetljive na komplement i brzo se razgrađuju.

Prikaz slučaja: Prikazujemo pacijentkinju staru 44 godine koja je decembra 2020. godine upućena hematologu UKC Niš zbog anemije i trombocitopenije. Inicijalni nalazi KKS Le 6,1x10⁹/L, Er 3x10¹²/L, Hgb 100 g/L, Hct 29,7 L/L, Tro 27x10⁹/L, Ret 6,4%, tbil 14,4 μmol/L, dbil 3,2 μmol/L, LDH 2623 U/L, AST 65 U/L, ALT 13 U/L, ferritin 188,9 μg/L, haptoglobin 0,04. Hemosiderin u urinu negativan. Hamov test negativan. Coombs test negativan. Marta 2021. godine imunofenotipizacija neutrofila periferne krvi implicira dijagnozu PNH zbog prisustva predominantno populacije PNH neutrofila oko 96,6% neutrofila. Maja meseca 2022. godine imala je površnu trombozu vena nogu a potom juna 2022. godine DVT. Pacijentkinja je lečena niskim dozama kortikosteroida uz LMWH potporu sem u hemolitičkim krizama sve do marta 2023. godine kada je započeto lečenje Ravulizumabom na Klinici za hematologiju UKC Srbije. Tok bolesti bio je praćen steroidnim DM na insulinskoj terapiji.

Zaključak: Primena kortikosteroida u lečenju bolesnice sa PNH smanjila je transfuzionu zavisnost i omogućila kontrolu parametara hemolize.

Ključne reči: kortikosteroidi, PNH, inhibitori komplementa

ABSTRACT

Introduction: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare acquired clonal disease of the hematopoietic stem cell caused by a somatic mutation of the *pigA* gene. This mutation affects the synthesis of glycosylphosphatidylinositol (GPI), leading to a deficiency of CD59 and CD55 proteins. Consequently, cells become hypersensitive to complement and are rapidly degraded.

Case report: A 44-year-old female patient was referred to a hematologist at UKC Niš in December 2020 due to anemia and thrombocytopenia. Initial findings included leukocytes 6.1x10⁹/L, erythrocytes 3x10¹²/L, hemoglobin 100 g/L, hematocrit 29.7 L/L, thrombocytes 27x10⁹/L, reticulocytes 6.4%, total bilirubin 14.4 μmol/L, direct bilirubin 3.2 μmol/L, lactate dehydrogenase 2623 U/L, AST 65 U/L, ALT 13 U/L, ferritin 188.9 μg/L, and haptoglobin 0.04. Tests for hemosiderin in urine, Ham's test, and Coombs test were negative. In March 2021, immunophenotyping of peripheral blood neutrophils confirmed PNH, showing 96.6% PNH neutrophils. In May 2022, she developed superficial thrombosis of the leg veins, followed by deep vein thrombosis in June 2022. The patient was treated with low doses of corticosteroids and low molecular weight heparin, except during hemolytic crises, until March 2023, when Ravulizumab treatment began. The disease course was managed with steroid-induced diabetes mellitus on insulin therapy.

Conclusion: The use of corticosteroids in PNH treatment reduced the patient's transfusion dependence and helped control hemolysis parameters.

Keywords: corticosteroids, PNH, complement inhibitors

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DIAGNOSIS AND TREATMENT OF ACUTE PAIN CRISIS OF A PATIENT WITH SICKLE CELL ANEMIA – CASE REPORT

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SAŽETAK

Uvod: Anemija srpastih ćelija je autozomno recesivno nasledno oboljenje koje se karakteriše proizvodnjom abnormalnog hemoglobina (HbS) i pojavom nefleksibilnih eritrocita oblika srpa. Odlikuje se anemijom, kraćim životnim vekom eritrocita, bolnim „krizama“, čestim infekcijama i trombozama.

Prikaz slučaja: Pacijent starosti 21 godinu sa istorijom lečenja srpaste anemije, javio se u Urgentni centar zbog bola u leđima sa propagacijom niz desnu nogu, koji je inicijalno pokušao da kupira visokom dozom diklofenaka. Na prijemu pacijent pod jakim bolovima, ikteričan, u prinudnom položaju, blago hipotenzivan, afebrilan. Nakon što je isključen neurološki uzrok bola, započeta je intravenska analgetska terapija, u vidu tramadola i metimazol natrijuma. U laboratorijskim analizama leukociti $16,9 \times 10^9/L$, hemoglobin 88 g/L, retikulociti 10,27%, dimer 4,28 ug/ml, bilirubini 154/13 umol/L, CK 4128 UI/ml, CRP 78 ng/ml. Tokom hospitalizacije na perifernom razmazu detektovani drepanociti, na ehosonografiji jetra 165 mm, uz negativne virusološke i imunološke analize. Tokom hospitalizacije dolazi do pada CK i d dimera ali i do dodatnog skoka CRPa do 187 ng/mL, i bilirubina do 487/252 umol/L. Bolesnik tretiran deplazmatisanim eritrocitima, hidroksikarbamidom, antibiotskom terapijom, intenzivnom rehidracijom, i po konsultaciji specijaliste za lečenje bola tramadolom (u dozi od 100 mg na 6h), metamizol natrijumom (u dozi 2,5 g na 12h) i morfinom (u početnoj dozi od 5 mg na 4h) uz paracetamol u probodu bola. Tek pri postizanju doze morfina od 90 mg dnevno (u režimu 15 mg na 4h) dolazi do kupiranja bola i normalizacije laboratorijskih vrednosti.

Zaključak: Akutna bolna kriza anemije srpastih ćelija izazov je u lečenju i zahteva multidisciplinarni pristup.

Ključne reči: drepanocitoza, bolna kriza, srpasti eritrociti

ABSTRACT

Introduction: Sickle cell anemia is an autosomal recessive hereditary disease characterized by the production of abnormal hemoglobin (HbS) and the appearance of inflexible sickle-shaped erythrocytes. It is characterized by anemia, a shorter lifespan of erythrocytes, painful “crises”, frequent infections and thrombosis.

Case report: A 21-year-old patient with a history of treatment for sickle cell anemia came to the Emergency Center because of back pain with propagation down the right leg, which he initially tried to treat with a high dose of diclofenac. On admission, the patient was in severe pain, icteric, in a forced position, slightly hypotensive, afebrile. In analyses, leukocytes $16.9 \times 10^9/L$, hemoglobin 88 g/L, reticulocytes 10.27%, d dimer 4.28 ug/ml, bilirubin 154/13 umol/L, CK 4128 UI/ml, CRP 78 ng/ml. During hospitalization, sickle cells were detected on the peripheral smear, on echosonography the liver was 165 mm. There was a drop in CK and d dimer with an additional rise in CRP to 187 ng/ml and bilirubin to 487/252 umol/L. The patient was treated with deplasmatised erythrocytes, hydroxycarbamide, antibiotic, intensive rehydration, and with tramadol (in a dose of 100 mg every 6 hours), metamizole sodium (in a dose of 2.5 g every 12 hours) and morphine (in an initial dose of 5 mg every 4 hours) with paracetamol. When a dose of morphine of 90 mg per day (in a regimen of 15 mg every 4 hours) was reached, pain relief was achieved with laboratory values normalization.

Conclusion: Acute painful crisis of sickle cell anemia is a challenge in treatment and requires a multidisciplinary approach.

Keywords: sickle cell disease, painful crisis, sickle erythrocytes

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DELAYED SEVERE HEMOLYTIC TRANSFUSION REACTION CAUSED BY ANTI FYA ANTIBODIES – CASE REPORT

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SAŽETAK

Uvod: Hemolizna transfuziona reakcija je retka, potencijalno fatalna komplikacija transfuzije.

Prikaz slučaja: Trudnica starosti 31 godine hospitalizovana je u Kliniku za ginekologiju i akušerstvo u 31. gestacijskoj nedelji zbog totalne placente previje. Prilikom prethodne komplikovane trudnoće i porođaja je bolesnica primala transfuzije deplazmatisanih eritrocita. Indikovao je hitan carski rez. Intraoperativni tok se komplikovao masivnim krvarenjem. Bolesnica je intraoperativno primila 1220 ml deplazmatisanih eritrocita i 638 ml autologne krvi prikupljene preko cell saver-a. Osmog postoperativnog dana u toku transfuzije deplazmatisanih eritrocita je došlo do razvoja povišene telesne temperature, jeze i drhtavice. Transfuzija je prekinuta i prijavljena je transfuziona reakcija. Narednog dana dolazi do pogoršanja stanja bolesnice, izražene malaksalosti, hipotenzije praćene pogoršanjem anemije (Hgb 48 g/L) sa laboratorijskim znacima hemolize, bez poremećaja hemostaze i bubrežne funkcije. Direktni antiglobulinski test nakon transfuzione reakcije je bio izrazito pozitivan (IgG+ C3d+) uz prisutna anti-Fya antitela. Primljen je metilprednizolon u dozi 2 mg/kg TM i ordinirane su tipizirane antigen negativne jedinice krvi uz ostale suportivne mere. Zbog daljeg pogoršanja opšteg stanja bolesnice i progresije hemolizne anemije (Hgb 28 g/L) ordinirani su intravenski imunoglobulini u dozi 1g/kg TM na koje dolazi do pada vrednosti bilirubina i LDH i stabilizacije hemoglobina. Ordinirano je još ukupno šest doza filtriranih eritrocita, bez znakova hemolizne reakcije. Doza kortikosteroida postepeno je smanjivana do obustave. Tokom daljeg višemesečnog praćenja, nalaz krvne slike se normalizovao.

Zaključak: Anti-Fya antitela najčešće dovode do blage hemolizne reakcije, ali u nekim slučajevima mogu dovesti do teške životno ugrožavajuće hemolizne reakcije.

Ključne reči: transfuziona reakcija, hemoliza, Duffy krvnogrupni sistem, anti Fya antitela

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ABSTRACT

Introduction: Hemolytic transfusion reaction is a rare, potentially fatal complication of transfusion.

Case report: A 31-year-old pregnant woman was hospitalized in the Clinic for Gynecology and Obstetrics in the 31st gestational week due to total placenta previa. During a previous complicated pregnancy and delivery, the patient received transfusions of packed red blood cells (PRBC). Emergency cesarean section was indicated. The patient had massive bleeding intraoperatively and received 1220 ml of PRBC and 638 ml of autologous blood collected through a cell saver. On the eighth postoperative day, during the transfusion of PRBC, the patient developed fever, chills, and shivering. Transfusion was discontinued, and transfusion reaction was reported. The following day, the patient's condition worsened with marked fatigue and hypotension, followed by worsening of anemia (Hgb 48 g/L) with laboratory signs of hemolysis without hemostasis disorders and renal dysfunction. The direct antiglobulin test after the transfusion reaction was strongly positive (IgG+ C3d+), and anti-Fya antibodies were present. Methylprednisolone was administered at a dose of 2 mg/kg BW, typed antigen-negative blood units were administered, along with other supportive measures. Due to further deterioration of the general condition and anemia progression (Hgb 28 g/L), the patient received intravenous immunoglobulins at 1g/kg BW, which decreased bilirubin and LDH values and stabilized hemoglobin. A total of six doses of filtered erythrocytes were given, with no signs of hemolytic reaction. The dose of corticosteroids was tapered until discontinuation. During follow-up for several months, the blood count normalized.

Conclusion: Anti-Fya antibodies generally lead to mild hemolytic reactions but sometimes cause severe life-threatening hemolysis.

Keywords: transfusion reaction, hemolysis, Duffy blood group system, anti Fya antibodies

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OUTCOME AND PREDICTORS OF MORTALITY IN CRITICALLY ILL PATIENTS WITH HEMATOLOGICAL MALIGNANCIES – RESULTS FROM A SINGLE CENTER

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SAŽETAK

Uvod: Prognoza bolesnika sa hematološkim malignitetima lečenih u jedinica-ma za intenzivno lečenje je loša. Zbog teškog opšteg stanja i komplikacija lečenja osnovne bolesti, mortalitet je izuzetno visok.

Cilj: Utvrditi preživljavanje i identifikovati prediktivne faktore lošeg ishoda bolesnika sa hematološkim malignitetima lečenih u jedinici za intenzivno lečenje.

Metode: Retrospektivno su analizirani podaci 144 bolesnika sa hematološkim malignitetima lečenih u Klinici za hematologiju koji su zbog hemodinamske i respiratorne nestabilnosti zahtevali nastavak lečenja u jedinici intenzivne nege Odeljenja urgentne interne medicine Kliničkog centra Vojvodine, u period od januara 2020. do juna 2024. godine.

Rezultati: Medijana ukupnog preživljavanja (OS) je bila 3 dana. Smrtnost nakon 28 dana od premeštaja je bila 82%. Univarijantnom logističkom regresijom, statistički značajan uticaj na preživljavanje nakon 28 dana su imali dijagnoza akutne leukemije ($p = 0,024$), sepsa prilikom premeštaja ($p = 0,0117$), vrednosti APACHE II ($p = 0,0065$) i SOFA skora ($p = 0,0007$), dužina hospitalizacije pre premeštaja ($p = 0,0103$), trajanje neutropenije ($p = 0,0334$), broj organa za potporu ($p = 0,0038$), potreba za vazoaktivnom potporom u prvih 24h ($p = 0,0097$) i kasnije ($p < 0,0001$), odnosno potreba za mehaničkom ventilacijom ($p < 0,0001$). Multivarijantnom logističkom regresijom, vrednost APACHE II skora preko 26 ($p = 0,0382$) i potreba za potporom više od dva organa u bilo kom trenutku od premeštaja ($p = 0,0431$) su bili statistički značajni prediktori OS ispitanika.

Zaključak: Veći mortalitet kod bolesnika primljenih u jedinicu intenzivne nege povezan je sa višim vrednostima APACHE II skora, potrebom za potporom organa i potrebom za mehaničkom ventilacijom. Smrtnost je veća kod bolesnika sa akutnom leukemijom u poređenju sa drugim hematološkim malignitetima.

Ključne reči: hematološki maligniteti, sepsa, APACHE, prognoza

ABSTRACT

Introduction: The prognosis of patients with hematological malignancies transferred to the intensive care unit (ICU) is historically poor. Due to the severe general condition and treatment complications of the underlying disease, mortality is high.

Objective: To determine survival and predictive factors of poor outcomes in hematological patients transferred to the ICU.

Methods: The data of 144 hematological patients transferred to the Department of Emergency Internal Medicine of the Clinical Center of Vojvodina from January 2020 to June 2024 were retrospectively analyzed.

Results: Median overall survival (OS) was three days. Mortality after 28 days from transfer was 82%. By univariate logistic regression, statistically significant impact on OS after 28 days had the diagnosis of acute leukemia ($p = 0.024$), sepsis on admission ($p = 0.0117$), APACHE II ($p = 0.0065$), SOFA score ($p = 0.0007$), duration of hospitalization before transfer ($p = 0.0103$), duration of neutropenia ($p = 0.0334$), number of supporting organs ($p = 0.0038$), need for vasoactive support in first 24h ($p = 0.0097$) and later ($p < 0.0001$), that is the need for mechanical ventilation ($p < 0.0001$). By multivariate logistic regression, the value of APACHE II score over 26 ($p = 0.0382$) and the need for support for more than two organs in any moment of transfer ($p = 0.0431$) were statistically significant predictors of OS.

Conclusion: Higher mortality in transferred patients is associated with higher prognostic score values and the need for organ support and mechanical ventilation. Mortality is higher in patients with acute leukemia compared to other hematological malignancies.

Keywords: hematologic neoplasms, sepsis, APACHE, prognosis

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ADULT LANGERHANS HISTIOCYTOSIS OF HIGH RISK LOCALIZATION

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SAŽETAK

Uvod: Histiocitoza Langerhansovih ćelija (LCH) je retka hematološka neoplazma sa incidencom od oko 1:1 000 000 u populaciji odraslih. Kliničke varijacije i stepen zahvatanja organa su veoma heterogene. U rizične forme pored multisistemskog oblika spada i lokalizovano zahvatanje kostiju lobanje. Dijagnoza se postavlja na osnovu kliničke slike, radioloških nalaza i biopsije.

Prikaz slučaja: Prvi pacijent je imao bolest lokalizovanu u parijetalnoj kosti sa endokranijalnom infiltracijom, dok je drugi pacijenti imao bolest koštanog sistema višestruke lokalizacije uz zahvatanje maksile. Lokalizacija bolesti kod oba pacijenta je rizična zbog visoke verovatnoće širenja i zahvatanja centralnog nervnog sistema. Inicijalno lečenje kod oba pacijenta je hirurški zahvat, a u nastavku primena hemioterapijskog LCHA1 protokola. Prvi pacijent je nakon 6 meseci primene hemioterapije u kompletnoj remisiji. Kod drugog pacijenta na evaluaciji nakon indukcione faze protokola verifikovana je progresija bolesti i trenutno je u toku analiza na BRAF V600 mutaciju radi eventualne primene vamorafeniba u nastavku lečenja.

Zaključak: Lečenje LCH je multimodalno i multidisciplinarno i sastoji se od kombinacije hirurgije, hemioterapije i radioterapije. Hemioterapijski protokol LCHA1 se koristi u slučajevima multisistemске bolesti i kada postoji lokalizovana bolest rizične lokalizacije. Protokol se sastoji od dve faze, prva je indukciona koja traje 6 nedelja uz obaveznu procenu odgovora, dok je druga konsolidaciona i ona traje između 6–12 meseci zavisnosti od odgovora na terapiju.

LCH rizične lokalizacije predstavlja kompleksan dijagnostički i terapijski problem koji zahteva promptno sprovođenje dijagnostičkih procedura i započinjanje sistemske terapije da bi se sprečila progresija bolesti. Odgovor nakon 6 nedelja terapije je značajan prognostički parametar u cilju evaluacije i eventualnog prilagođavanja terapije.

Ključne reči: Langerhansova histiocitoza, osteonekroza, ulceracija gingiva

ABSTRACT

Introduction: Langerhans cell histiocytosis (LCH) is a rare hematological neoplasm with an incidence of about 1:1,000,000 adults. Clinical presentation and the degree of organ involvement is exceptionally varied.

Case presentation: The first patient presented with a lesion in the parietal bone with endocranial infiltration, the second had multiple bone lesions including the maxilla. Both of these bones are regarded as high-risk because of the high probability of further central nervous system involvement. Firstly, a surgical excision was performed and was followed by chemotherapy using the LCHA1 protocol. The first patient was in complete remission after 6 months of treatment, while the second had verified disease progression after 6 weeks of treatment. Currently, we are evaluating the presence of the BRAF V600 mutation in order to continue the treatment using vamorafenib.

Conclusion: The treatment of LCH has been often multimodal and multidisciplinary and requires a combination of surgery, radiotherapy and chemotherapy. LCH1 protocol for adults can be used in patients presenting with multisystem disease and in patients that have high-risk localized disease. The protocol consists of two phases; the first phase is a 6 week long induction phase followed up with response evaluation while the second phase is maintenance therapy lasting 6–12 months depending on the response.

LCH of high-risk localisation poses a complex diagnostic and therapeutic problem which requires prompt patient evaluation and initiation of systemic therapy to stop disease progression. Response after 6 weeks is a strong prognostic marker and should be evaluated to assess the need for a change in therapy.

Keywords: Langerhans cell histiocytosis, osteonecrosis, gingival ulceration

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ANTIMICROBIAL RESISTANCE AND THE OUTCOME OF TREATMENT OF INFECTIONS IN HEMATOLOGICAL PATIENTS

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SAŽETAK

Uvod: Bakterijske infekcije krvi i urina i dalje predstavljaju glavni uzrok morbiditeta i mortaliteta kod bolesnika sa hematološkim malignitetima.

Cilj: Utvrditi prisustvo i učestalost rezistencije izolovanih bakterija na antimikrobne lekove, kao i ishod lečenja infekcija kod bolesnika sa hematološkim malignitetima.

Metode: Retrospektivno je analizirano 199 pozitivnih mikrobioloških izolata bolesnika sa hematološkim malignitetima lečenih u Klinici za hematologiju UKCV, u periodu od januara 2023. do juna 2024. godine.

Rezultati: Od ukupnog broja pozitivnih mikrobioloških izolata, 78 (39,2%) su činile hemokulture, a 64 (32,2%) urinokulture. Gram negativne (GN) bakterije su izolovane iz 64,1% hemokultura, odnosno u 78,9% svih izolata. Najčešći GN izolat je bila *Klebsiella pneumoniae* u 32% hemokultura, 22,1% svih izolata. Panrezistentne bakterije (PDR) su izolovane u 26,9% slučajeva hemokultura, odnosno 39,7% slučajeva svih izolata. Ostale pozitivne izolate su činili multirezistentni (MDR) uzročnici. Univarijantnom logističkom regresijom, izolat *Acinetobacter baumannii* i PDR uzročnika iz hemokulture su bili statistički značajno povezani sa smrtnim ishodom ($p = 0,0041$ vs. $p = 0,0116$). Multivarijantnom logističkom regresijom je izolat PDR uzročnika bio statistički značajno povezan sa smrtnim ishodom ($p = 0,0257$). Posmatrajući sve izolate, pozitivna hemokultura ($p = 0,0378$) i urinokultura ($p = 0,0196$), izolat *Acinetobacter baumannii* ($p = 0,0209$) i PDR bakterija ($p = 0,0003$) su univarijantnom analizom bile statistički značajno povezane sa smrtnim ishodom, dok je multivarijantnom logističkom regresijom utvrđena statistički značajna povezanost PDR izolata i pozitivne hemokulture sa smrtnim ishodom ($p = 0,0007$ vs. $p = 0,0278$).

Zaključak: Veći mortalitet povezan je sa izolatom *Acinetobacter baumannii* i PDR uzročnika u hemokulturama kod naših bolesnika sa hematološkim malignitetima.

Ključne reči: antimikrobni agensi, hematološki maligniteti, multirezistentni uzročnici, panrezistentni uzročnici

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ABSTRACT

Introduction: Bloodstream and urine infections are still the main cause of morbidity and mortality in patients with hematological malignancies.

Objective: To determine the presence and frequency of bacterial resistance to antimicrobial drugs and the infection outcomes.

Methods: We retrospectively analyzed 199 positive microbiological isolates from hematological patients treated at the Clinic of Hematology, Clinical Center of Vojvodina, from January 2023 to June 2024.

Results: Out of the total isolates, 78 (39.2%) were hemocultures, and 64 (32.2%) were urine cultures. Gram-negative (GN) bacteria were isolated from 64.1% of hemocultures and 78.9% of all isolates. The most common GN isolate was *Klebsiella pneumoniae* in 32% of hemocultures and 22.1% of all isolates. Pan-resistant bacteria (PDR) were isolated in 26.9% of hemocultures, and 39.7% of all isolates. Other positive isolates were multidrug-resistant (MDR) pathogens. By univariate logistic regression, *Acinetobacter baumannii* isolates, and PDR agents from hemocultures were statistically associated with death ($p = 0.0041$ vs. $p = 0.0116$). By multivariable logistic regression, the isolate of PDR agents was statistically significantly associated with the death outcome ($p = 0.0257$). Observing all isolates, positive hemocultures ($p = 0.0378$), urine cultures ($p = 0.0196$), *Acinetobacter baumannii* isolate ($p = 0.0209$), and PDR bacteria ($p = 0.0003$) were statistically significantly associated with the death by univariate analysis. At the same time, multivariable logistic regression determined a statistically significant association of PDR isolates and positive hemocultures with death ($p = 0.0007$ vs. $p = 0.0278$).

Conclusion: Higher mortality is associated with the isolation of *Acinetobacter baumannii* and PDR agents in hemocultures in hematological patients.

Keywords: antimicrobial agents, hematologic malignancies, multidrug resistance, pandrug resistance

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CIP - Каталогизacija u publikaciji
Народна библиотека Србије, Београд

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SRPSKI medicinski časopis Lekarske komore

= Serbian journal of the Medical chamber / glavni i odgovorni urednik Milena Šantrić-Milićević. - [Štampano izd.]. - Vol. 1, br. 1 (sep. 2020)- . - Beograd : Lekarska komora Srbije, 2020- (Novi Sad : Sajnos). - 30 cm

Tromesečno. - Tekst na srp. i engl. jeziku. - Drugo izdanje na drugom medijumu: Srpski medicinski časopis Lekarske komore (Online) = ISSN 2737-9752

ISSN 2737-971X = Srpski medicinski časopis Lekarske komore (Štampano izd.)

COBISS.SR-ID 19685641